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Screening for distant metastases in
head and neck cancer patients using
¹⁸F-FDG-PET and chest CT

A.Senft

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Chapter 1

General introduction

1. Head and neck cancer

1.1 Head and neck carcinomas

1.1.1 Etiology and risk factors

Head and neck squamous cell carcinoma (HNSCC) accounts for approximately 5% of all malignant tumours worldwide. Every year, more than half a million new cases of head and neck cancer of the oral cavity, pharynx, or larynx are diagnosed worldwide (1,2). In The Netherlands, in 2014 a total of 2955 developed malignancies in the upper aero digestive tract (3). The most important risk factor for developing head and neck cancer is cigarette smoking and other means of tobacco consumption. Alcohol abuse is also considered to be a large contributor. Especially pharyngeal carcinomas, cancer of the supra-glottis and oral cavity have a strong association with heavy alcohol consumption. The combination of heavy tobacco and alcohol use increases the risk for developing head and neck cancer exponentially. Other associations with HNSCC are genetic predisposition, infections with Human Papilloma Virus (HPV) and Epstein-Barr Virus (EBV), occupational exposure and poor oral hygiene (4-16).

1.1.2 Staging and Treatment

Head and neck cancer is staged according to the TNM system of the International Union Against Cancer / American Joint Committee on Cancer (17). This classification describes the anatomical extent of the primary tumour as well as the involvement of regional lymph nodes and distant metastases (18) and is used for clinical staging in four categories (I-IV). About one-third of the patients present with early stage (I-II) disease (19) and are usually treated with surgery or radiotherapy. Two third have advanced stage HNSCC and usually are treated with surgery and radiotherapy with or without chemotherapy or with a combination of chemotherapy and radiotherapy with salvage surgery in reserve.

1.1.3 Primary tumour

Approximately 90% of the HNSCC originate from any part of the lining mucosa in the head and neck region. Discrimination of anatomical areas has led to definition of different HNSCC sites: lip and oral cavity, oro-, hypo- and nasopharynx, larynx, nasal cavity and paranasal sinuses and unknown primary carcinoma. Other sites include malignant melanoma of the upper aerodigestive tract, major salivary glands and thyroid gland. For each of these sites, a classification for the T-stage has been made. Size and extension are determinants for primary tumour staging. Accurate staging is important for determining the choice of treatment.

1.1.4 Second primary tumour

The development of second primary tumours is strongly associated with long-term tobacco and excessive alcohol exposure. Smokers have a 5 times increased risk, whereas with alcohol abuse the risk is doubled (20). A prior history of previous HNSCC remains

one of the strongest predictors of head and neck cancer. The definition of a second primary tumour (SPT) is still subject of debate. In general, tumours are considered SPT when occurring more than 2 centimeters away from the primary tumour and arising after 3 years or more. Although second field tumours may meet these criteria they are not to be considered SPT due the fact that these tumours arise from the same genetically altered field as the index tumour (21). HNSCC tumours mostly metastasize to the lungs and should be distinguished from SPT: metastases are usually subpleurally located, multiple and at the end of a blood vessel, whereas SPT is solitary and centrally located.

Occurrence of SPT can be synchronous or metachronous. Synchronous if they appear at the same time or within 6 months of the index tumour and metachronous if developed after 6 months (22). SPT is associated with poor prognosis especially when localized in unfavorable sites in lungs or oesophagus (23). Also SPT often arises in previously irradiated or operated areas. The choices of treatment are then limited by the treatment of the index tumour i.e., radiation or prior surgery. Detection of simultaneous SPT is of great clinical importance; both primary tumour and SPT can be treated at the same time.

1.2 Distant metastases

The incidence of distant metastases in HNSCC is relatively low but remains a major determinant of prognosis and is therefore an important factor in clinical decision making. Distant metastases usually occur late in the course of the disease and are mostly localized in the lungs (45-83%), bone (10-41%) and liver (6-24%). The incidence of distant metastases at presentation varies from 5 to 17% (24-26). The incidence of clinically detected distant metastases in HNSCC is 4 to 26%, while at autopsy higher incidences have been reported (37-57%) (27-30). Patients with distant metastases are generally considered not curable and almost always receive only palliative treatment (31).

In recent years risk factors for developing distant metastases were identified: three or more lymph node metastases, bilateral or low-jugular metastases, metastases larger than 6 centimeters, regional recurrence or second primary tumours. Screening for distant metastases has been performed with the use of multiple modalities; laboratory biochemical tests to identify bone and liver metastases, X-ray and CT to detect lung metastases, bone scintigraphy for detection of spreading to the skeletal system and ultrasound or CT for liver metastases. Of these diagnostic tools CT of the chest proved to be the most valuable in screening for distant metastases (32).

Despite negative screening and locoregional control some patients develop distant metastases. It is assumed that these distant metastases were already present during initial diagnostic work-up, but were apparently below the detection limit of screening tests. If distant spread occurs shortly after major surgery with curative intent these patients probably underwent futile extensive treatment (33). Roughly 90 percent of the patients with distant metastases will die within 12 months.

2. Positron Emission Tomography

2.1 General principles

Mostly used screening modalities in head and neck cancer patients are anatomical techniques. For example, X-ray computed tomography (CT) uses tissue dependent absorption of X rays whereas magnetic resonance imaging (MRI) uses proton densities or relaxation times in an externally induced magnetization. Estimates of size and structure change compared to normal tissue can hence be assessed. PET detects the distribution, and dynamic redistribution, of specific tracers, whose properties are tailored to be sensitive to monitor specific biochemical and physiological processes. The PET scan is therefore a functional imaging technique based on a combination of advanced detection equipment and the use of radioactive markers. Radioactive isotopes send out positrons, which are the antimatter counterpart of electrons and therefore have the same mass but a positive charge. As positrons travel through matter, they lose energy through ionization and excitation of nearby atoms and molecules. After losing enough energy and travelling a distance of about 2 to 3 mm, the positron encounters an electron and annihilation occurs. This causes the release of two gamma ray photons with an energy of 511 keV, emitted at an angle of 180°. This emission in opposite direction is the basis of coincidence imaging. The gamma rays are simultaneously detected by a ring of detectors (coincidence-detection). It is possible to localize the source of emission along this straight line of coincidence, also called the line of response.

Modern generation cameras are even able to calculate the annihilation point by measuring the difference between the times of flight of the photons. Detection is ideally performed by a dedicated full ring detector, but a dual-head 'hybrid' coincidence gamma camera yielding a lower sensitivity for detection of the photons can also be used (34-38).

Viewing of the scans is mostly performed visually, although (semi-)quantified methods are used as well. The detection of lesions is based on the differences between tracer uptake in a lesion and of the surrounding normal tissue (36). Lesions of 4 mm and larger can be detected by the PET scan, depending on the location and pathological properties.

2.2 Tracers

Different positron emitting radioactive isotopes can be used for PET scanning. These isotopes can substitute the corresponding stable isotopes in relevant biomolecules. This leads to a wide class of PET tracers whose in vivo behavior is unaltered in comparison to their naturally occurring counterparts (34,39). The label can also replace other chemical elements in the molecular structure, for example ^{18}F can replace hydrogen in many organic compounds. This approach leads to PET tracers whose chemical properties are different from native substances which makes it possible to create tracers with special properties such as enhanced trapping in a target lesion. A good example of this is the glucose

analogue deoxyglucose labelled with fluorine-18 (^{18}FDG) (34). It has the same uptake capacity as glucose in cancer cells, however after phosphorylation ^{18}FDG -6 phosphate is not recognized as a substrate for further metabolic degradation (glucolysis) or storage in glycogen. Therefore in the absence of sufficient activity of the enzyme its exit from the cells is prevented. Glucose uptake is high in brain cells, muscle cells, inflammatory tissues (macrophages, plasma cells, lymphocytes and granulocytes) and most types of tumour cells. However some tumours have less to none uptake of ^{18}FDG , e.g. neuro-endocrine tumours.

2.3 Applications

^{18}FDG -PET is used in cardiology and neurology, but mostly in the oncologic field, where it is commonly used for primary staging and restaging after therapy. The technique has a high sensitivity in FDG avid tumour types, allowing the detection of tumours with a diameter of 4 mm (depending on location and FDG avidity). Additionally, ^{18}FDG -PET has the ability to differentiate between vital tumour tissue and fibrosis or necrosis following therapy, yielding a higher specificity compared to conventional imaging techniques (CT and MRI)

In the oncologic field, ^{18}FDG -PET is used in the diagnostic work-up of patients with non-small cell lung cancer, malignant lymphomas, melanomas, gastro-intestinal carcinomas and squamous cell carcinomas of the head and neck.

2.3.1 ^{18}FDG -PET in head and neck

The optimal use of ^{18}FDG -PET in head and neck tumours is still being investigated.

Occult primary tumours: Patients may present with lymph node metastasis as first symptom of illness. In most patients a primary tumour can be identified using extensive diagnostics. In 1.5-3% of HNSCC patients, however, the primary tumour remains occult. ^{18}FDG -PET studies show additional value for the detection of a primary tumour in 21-47% of these patients (40,41).

Lymph node metastases: Detection of lymph node metastases in the neck which are proven through biopsy are an important step in decision making for the best possible treatment. The usage of ^{18}FDG -PET in screening the neck has a sensitivity of 74-93% with a specificity of 93-94%. In comparison to CT, MRI and ultrasound, ^{18}FDG -PET appeared to be more reliable (42,43). However, in the clinically negative neck, ^{18}FDG -PET has a sensitivity of about 50% and is therefore less useful concerning the detection of occult (micro) metastases (44,45).

Distant metastases and second primary tumours: The detection of distant metastases or second primary tumours will change the choice of treatment in head and neck cancer patients. The use of PET, which is a whole body technique, may add value in screening for distant metastases.

Tumour response prediction to non-surgical treatment: Organ preservation treatment (radiotherapy with or without chemotherapy) has become increasingly important in head and neck oncology. As ^{18}F FDG-PET detects biological parameters in tissue, it may be able to give prognostic information of tumour response, both in the pretreatment phase and in an early phase of treatment. An early identification of nonresponders to (chemo)radiation would refrain a substantial number of patients from the morbidity and costs of a futile extensive treatment and the complications of salvage surgery and may improve survival due to the remaining option of postoperative irradiation. Studies on this subject are not unambiguous, although some show promising results (46-49).

Response evaluation after non-surgical treatment: If non-surgical treatment fails, it is important to detect residual or recurrent disease as soon as possible for the highest chance of successful salvage treatment. Therefore, routine response evaluation is performed during follow-up. ^{18}F FDG-PET is better than anatomical imaging (e.g. CT and MRI) for response evaluation 3 months after chemoradiation for advanced stage HNSCC (50,51).

Residual tumour after non-surgical treatment: Radiotherapy with or without chemotherapy changes the anatomy of tissues resulting in a difficulty differentiating residual tumour from fibrosis, oedema or necrosis on CT or MRI. In residual mass of the neck, negative aspiration cytology does not rule out vital tissue. Neck dissection shows in roughly 40% no vital tumour, and has a high risk of post-operative complications after (chemo)radiation. Studies using ^{18}F FDG-PET to discriminate between residual tumour and post-(chemo)radiation changes show promising results, but need to be extended (50,52-55).

Tumour recurrence after non-surgical treatment: Laryngeal and pharyngeal carcinomas are often treated with radiation therapy with or without chemotherapy. Organ preservation is a primary goal without compromising locoregional disease control. Approximately 50% of patients with severe oedema or necrosis following radiotherapy will have a recurrence. Performing a biopsy itself can present a dilemma as this may exacerbate postradiotherapy changes. ^{18}F FDG-PET already has a role in detecting recurrent laryngeal carcinoma in this setting (56).

Planning of radiotherapy: In radiotherapy, setting exact limits for the target-volume, has become even more important with the introduction of 'three-dimensional conformal radiation therapy' and 'intensity-modulated radiation therapy', to reduce the impact on healthy surrounding tissue. Comparing tumour-volumes estimated by CT, MRI and ^{18}F FDG-PET showed promising results for the latter technique, and most likely especially for ^{18}F FDG-PET-CT (57).

3. Screening, efficiency and statistics

3.1 Screening

Screening can be defined as routine testing of people that do not show any signs of the disease being tested. Wilson and Jungner made directives about screening in 1968 for the World Health Organization (58). These state that screening a healthy population is useful when the disease is an important health risk, the mechanism of the disease is well understood and there should be a detectable early stage that can be treated better than more advanced stages. Effective and acceptable tests are to be used to detect early stages in which the interval between different tests must be stated. The extra amount of work for the health care system should be counter measured adequately. The physical and psychological risks should be minor compared to the benefits and the cost should be balanced to the benefits (59).

The effect of screening is often difficult to investigate. In cancer research the only true outcome is death. Since this may take a long follow-up it is easier to take an intermediate end-point. This however may lead to inaccuracies, such as lead time bias (diseases discovered through screening at an earlier stage), length time bias (only the slowly progressive form of the disease is found during screening and overdiagnosed bias (during screening disease is found that would otherwise not have become clinically significant) (60-62).

In the Netherlands as in many countries in Western Europe and the USA nationwide screening programs are active for breast and cervical cancer (61,63,64). The effect, risks and harms of these programs are still subject of discussion, which based on the aforementioned known biases, focuses on the health and survival benefits of screening for both the individual and society as a whole compared to the risks. The main problem seems to be that screening is performed in a healthy, low risk population. It might be more useful to screen a population that is at risk, for example HPV positive patients for cervical cancer (59,61,63-65). We performed this form of screening in a population at risk, to detect distant metastases in patients with advanced stage head and neck cancers. Our aim of screening was not to find early stage curable disease but to detect disseminated disease without curative options to prevent the patients from undergoing futile extensive treatment and provide the patients with the best quality of life as possible. In literature screening and staging are often used to indicate similar meaning, where in fact they are not interchangeable. Looking for distant metastases of a given primary tumour should be considered staging, whereas looking for second primary tumours is a screening process. However, in this thesis we will use screening also for detection of distant metastases in HNSCC patients.

3.2 Cost effectiveness and efficiency

Due to an increasing focus on costs in health care during these last few decades, the government, health insurances and medical professionals emphasize the importance of

guidelines that promote cost-effectiveness (66). The primary goal of guidelines is to close the gap between what clinicians do and what scientific evidence supports. There is a worldwide interest in clinical guidelines which originates from issues faced by most healthcare systems: rising costs; variation in service delivery which presumably is caused by inappropriate care; the intrinsic desire of healthcare professionals to offer and patients to receive the best care possible (67). There is a difference in interest between society and the individual concerning cost-effectiveness. The value of one's life is nearly infinite for the individual, while society places a far more conservative value in our lives; disease causes economic loss due to missed days of work or early death (68). In continuation of this, there are 5 types of costs: direct costs within healthcare, direct costs outside healthcare, indirect costs within healthcare, indirect costs outside healthcare and intangible costs. The direct costs within healthcare include the actual amount of the health services resources directly involved in illness diagnosis and treatment. Direct costs outside healthcare include patients costs like travelling costs. Indirect costs within healthcare are medical costs of disease not related to the therapy under study which arise as a consequence of life years gained. Indirect costs outside healthcare involve the economic loss of a worker's production secondary to the illness. The intangible costs of disease are described as the changes in the quality of life for the patient and family (69-72).

Incorporating economic considerations into guidelines up to date still provides difficulties. However it is clear that healthcare is expensive while resources are limited and therefore diagnostics and effects of treatment should be in balance with total costs. Economic evaluation can be looked at in 3 ways; first, a cost-identification analysis in which the financial consequences for providing care according to the guidelines is outlined. In this, all outcomes should be equivalent in terms of quality of life, survival and functional indices. The costs are the only metric examined. Second, a cost-effectiveness (or cost-utility) balance can be performed in which the costs of an intervention are measured against a particular intervention or effect. A separate balance can be made for each effect. These measured effects can be diagnosing a patient with a disease, longer survival or better quality of life. It is not easy to calculate a cost-effectiveness balance. The effect is calculated against a reference script and should consist of the diagnostics or treatments used in best practice. Third, a cost-benefit analysis produces a ratio of the costs to an estimation of the monetised benefit of an intervention (66,67,73).

Due to the fact that cost analyses are complex and difficult to perform it is highly unlikely that cost analyses measure up to the ideal standards of society perspective, outcome measurement, comprehensive accounting of costs, appropriate comparison interventions, discounting cost over time and sensitivity analysis for uncertainty. However a cost analysis with acknowledged imperfections is preferable to none (74).

3.3 Statistics

The accuracy of the diagnostic modalities used for screening was calculated by comparing the results of the test under evaluation with the results of a reference standard. This

standard is regarded as the best available modality to establish the presence or absence of disease, and mostly consists of a combination of histopathology and follow-up. The results are analyzed in a 2x2 table, in which the results of the new diagnostic test are compared to the results of the reference standard. This table is then used to calculate outcome measures such as sensitivity, specificity, positive predictive value, negative predictive value and accuracy. Sensitivity is the chance of a positive result in a patient with malignant tumour, while specificity is the chance of a negative result in a tumour negative patient. Positive predictive value shows the probability of actually having a positive event (e.g. distant metastases or second primary tumour) when having a positive test result. Negative predictive value shows the probability of not having tumour when having a negative test result.

The pairs of sensitivity and specificity of each study were plotted in receiver operating characteristic (ROC) space. Sensitivity (percentage of true positives) is plotted against the percentage of false positive (1-specificity, defined as the percentage of true negatives). The Q-point is the maximum joint sensitivity and specificity, closest to the optimal upper left corner of the summary ROC curve, resulting in a larger area under the curve. Logistic regression analysis was performed to determine which diagnostic technique has the most impact on outcome. The overall quality of the test performance is reflected by its ability to raise the sensitivity without compromising the specificity (62).

Where interobserver variability is determined a weighted kappa is used. This shows the level of agreement between the observers, beyond the level expected by chance. The higher the weighted kappa, the higher the level of agreement, with a maximum of 1.0.

Where estimates of survival functions are calculated the Kaplan-Meier method is used for each risk factor and per number of risk factors and compared via the log-rank test. For multi-variate analysis a Cox regression analysis is used, with the method of "Forced entry". These models enable the quantification of the influence of the predictive variables with regard to the development and time to detection of distant metastases on survival.

4. Aim of the study and outline of these thesis

In order to detect distant metastases and second primary tumours in head and neck cancer patients new imaging techniques have been developed in the last decades. In case of disseminated disease patients are often considered incurable and palliative care is the only option. To prevent patients from undergoing extensive and often futile treatment, optimization in screening for distant metastases is required.

The aims of the research described in this thesis were to evaluate the daily practice and the possibilities of imaging techniques in order to detect distant metastases in patients with primary head and neck carcinomas.

Chapter 2 describes a multi-center prospective trial in which screening for distant metastases in head and neck cancer using ^{18}F FDG-PET and chest CT is performed. The accuracy of both screening modalities separately and the combination of both modalities combined was calculated in order to find the optimal screening tool.

Chapter 3 describes a cost-effectiveness analysis comparing CT chest, ^{18}F FDG-PET and the combination of both when screening for distant metastases in head and neck cancer patients.

In **Chapter 4** interobserver variability was calculated for Chest CT and whole body ^{18}F FDG-PET in screening for distant metastases in head and neck cancer patients.

Chapter 5 describes a validation of an algorithm for the use of CT chest and whole body ^{18}F FDG-PET in screening for distant metastases and second primary tumours in head and neck cancer patients.

In **Chapter 6** previously identified high risk factors for development of distant metastases in head and neck cancer patients were validated. Also the impact of time of detection of distant metastases on survival was investigated.

Chapter 7 describes the impact of surveillance intervals on the sensitivity of FDG-PET/CT for the detection of distant metastases in head and neck cancer patients.

In **Chapter 8** we performed a survey to evaluate the current practice and change in practice concerning screening for distant metastases in head and neck cancer patients.

Chapter 9 contains the general discussion and future perspectives.

In **Chapter 10** this thesis is summarized in English and Dutch.

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Chapter 2

Screening for distant metastases in head and cancer patients by chest CT or whole body ^{18}F FDG-PET: A prospective multicenter trial

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Abstract

The aim of the study was to define the added value of whole body ^{18}F FDG-PET in screening for distant metastases in patients with head and neck squamous cell carcinoma (HNSCC) and risk factors. In a multi-center prospective study between 1998 and 2003, 145 consecutive HNSCC patients with risk factors for distant metastases underwent chest CT and whole body ^{18}F FDG-PET for screening for distant metastases. The data of 92 evaluable patients who developed distant metastases or who had a follow-up of at least 12 months were analyzed. Besides their performance in clinical practice, the operational characteristics of PET and CT using ROC analyses were investigated. Pretreatment screening identified distant metastases in 19 patients (21%). ^{18}F FDG-PET had a higher sensitivity (53% vs. 37%) and positive predictive value (80% vs. 75%) than CT. The combination of CT and ^{18}F FDG-PET had the highest sensitivity (63%). The ROC analyses of the five point ordinal scales revealed that the “area under the curve” (AUC) of ^{18}F FDG-PET was significantly higher as compared to CT. In HNSCC patients with risk factors, pretreatment screening for distant metastases by chest CT is improved by ^{18}F FDG-PET.

Introduction

Head and neck squamous cell carcinoma (HNSCC) accounts for approximately 5% of all malignant tumors worldwide. Two thirds of the patients with HNSCC present with advanced disease. HNSCCs preferentially metastasize to regional lymph nodes rather than spread hematogenously. Distant metastases usually occur late in the course of the disease. As results of locoregional treatment have improved significantly over the last decades, more patients are at risk to develop second primary tumours and distant metastases (1).

The presence of distant metastases at initial evaluation influences the prognosis and thus treatment selection: since no effective systemic treatment for disseminated HNSCC is currently available, patients with distant metastases are generally not considered curable and often receive only palliative treatment. Overall survival for patients with distant metastases detected at initial screening is significantly poorer compared to patients with distant metastases missed during initial screening and detected during follow-up (2). Therefore, screening for distant metastases is important to avoid futile extensive treatments.

The reported incidence of clinically identified distant metastases in HNSCC at presentation varies from 2 to 18% (2-5), but this is generally considered too low to warrant routine screening for distant metastases in all HNSCC patients (3,6). This incidence is directly related to the stage of disease, particularly to the presence and extension of lymph node metastases and locoregional control and depends on the applied diagnostic methods (2, 6-9). Jäckel and Rausch (5) found that screening is particularly useful in patients with advanced stage disease, local and/or regional recurrences and second primary tumours below the clavicles. Loh et al. (10) found T4 and/or N2 or N3 oropharyngeal, hypopharyngeal and supraglottic squamous cell carcinoma to be risk factors for the development of distant metastases. In previous studies, we refined these risk factors, found that bone scans and ultrasound/CT of the liver did not add to chest CT in screening for distant metastases (3), and validated this in a prospective follow-up study (2). At the same time, this evaluation showed that 20% of these high risk patients who had a negative CT-screening at presentation developed distant metastases within 12 months after therapy with curative intent. In one-third of the cases, these missed distant metastases were extrathoracic (2). Therefore, a more sensitive 'whole-body' technique might be useful. Positron emission tomography (PET) using the radiolabeled glucose analog ^{18}F -fluorodeoxyglucose (FDG) has such a potential (11). The aim of the present study was to investigate the potential added value of whole body ^{18}F FDG-PET in screening for distant metastases in HNSCC patients with risk factors.

Materials and Methods

Between 1998 and 2003, we performed a multi-center (VU University Medical Center Amsterdam, University Medical Center Groningen and Radboud University Nijmegen

Medical Centre) prospective observational study. Attending head and neck surgeons considered 145 patients eligible for the study. Inclusion criteria were: 1. HNSCC, 2. candidates for extensive treatment with curative intent (surgery and/or radiotherapy with or without chemotherapy), 3. at increased risk for distant metastases (i.e.: ≥ 3 lymph node metastases ($n=20$), bilateral lymph node metastases ($n=36$), lymph node metastases of ≥ 6 cm ($n=30$), low jugular lymph node metastases ($n=6$), regional tumour recurrence ($n=10$) and second primary tumours ($n=25$), as assessed by palpation, CT, MRI, and/or ultrasound-guided fine-needle aspiration cytology (3). All patients gave written informed consent. The protocol was approved by the institutional review boards and ethics committees.

After exclusion of patients who were incorrectly included or had logistical problems, 111 patients remained (Figure 1). Since the reference standard for further data analysis was detection of distant metastases or negative follow-up of 12 months (see Data analysis), we excluded 19 patients who died without distant metastases within these 12 months follow-up. Therefore, we obtained evaluable data in 92 patients. Results of the first 35 patients have been published elsewhere (11.) Of these 92 patients, 70 were male, the mean age was 59 years (range 44 - 81). Primary tumour sites were the oral cavity ($n=20$), oropharynx ($n=30$), hypopharynx ($n=16$), larynx ($n=17$), cervical esophagus ($n=3$) and lymph node metastases of an unknown primary tumour ($n=19$). Eleven patients had more than one synchronous primary tumour.

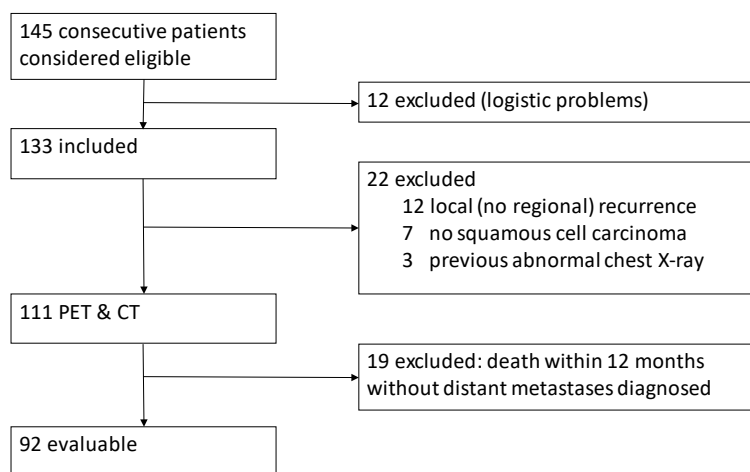


Figure 1. Inclusion of patients.

Imaging techniques

All patients underwent chest CT and ^{18}F FDG-PET, in random order as dictated by logistics. Spiral CT scans were obtained with a fourth-generation Siemens Somaton Plus (Siemens AG, Erlangen, Germany after intravenous administration of contrast medium (Ultravist, Schering AG, Berlin, Germany). Contiguous axial scanning planes were used with a 5-mm

slice thickness. Radiological criteria for lung metastases were: smoothly defined and sub-pleurally located lesions, multiple and located at the end of a blood vessel (12); for bronchogenic carcinoma, solitary, spiculated, and centrally located lesions; and for mediastinal lymph node metastases, a short axial diameter of more than 10 mm. ^{18}F FDG-PET was performed after patients had fasted for 6 hours with ample access to water. At 60-90 minutes after the intravenous administration of 250-370 MBq ^{18}F FDG, imaging of trajectory knee-skull base was performed using a dedicated full ring BGO PET scanners (Amsterdam/Groningen: CTI/Siemens ECAT HR+, Nijmegen: CTI/Siemens ECAT EXACT). Any focal abnormality, suspicious for malignancy was reported.

Data analysis

The result of the clinical diagnostic work-up between presentation until a follow-up of 12 months was used as reference standard, and patients were classified as positive or negative with respect to the presence of distant metastases. Follow-up was performed by regular (each 6 weeks in the first year) visits to the outpatient clinic. During follow-up, the dates of the detection of distant metastases, second primary tumours and/or death were recorded. Although the primary goal was screening on distant metastases, second primary tumours were also registered.

CT- and ^{18}F FDG-PET-scans were evaluated by different attending staff radiologists and nuclear medicine physicians, respectively, according to common clinical practice, and without knowledge of the result of alternative scan modality. For clinical decision making, these scans were scored either positive or negative. Initial screening was classified as true positive if there were evident metastases on chest CT, if lesions on chest CT were progressive or if biopsy (obtained by bronchoscopy, thoracoscopy, or thoracotomy) revealed metastasis. ^{18}F FDG-PET was considered true positive if a site of increased uptake proved malignant by histopathology or abovementioned conventional diagnostic techniques. If chest CT or ^{18}F FDG-PET had been abnormal during initial screening but further pre-operative work-up had remained inconclusive, patients were treated as scheduled. If follow-up of 12 months did not reveal metastases, such suspicious CT or ^{18}F FDG-PET results were classified as false-positive. If a patient had a negative chest CT or ^{18}F FDG-PET, but developed distant metastases during follow-up of 12 months, screening was considered false-negative. Screening by chest CT or ^{18}F FDG-PET was true-negative if a patient had negative test results and no distant metastases were observed within 12 months.

Patients with negative screening results and manifest distant metastases within 12 months of follow-up were stratified for presence or absence of locoregional control, because no distinction can be made between growth of subclinical metastases already present at time of screening and reseeding by an eventual locoregional recurrence. Further, intrathoracic lesions were analyzed separately, since only these tumours can be detected by CT-scan of the chest as well as whole body ^{18}F FDG-PET. Since the primary aim of the screening is to detect distant metastases, and detection of second primary tumours is an

additional, but clinically relevant finding, patients with second primary tumours found during screening or follow-up were analyzed separately.

Scenario analyses

As stated before, 19/111 included patients could not be evaluated because of death or loss to follow-up within 12 months without established development of distant metastases. It is therefore unknown whether these patients would have developed distant metastases if they had completed the follow-up period of 12 months. To illustrate the impact of this situation, we analyzed the data in a “best case” and a “worst case scenario”, assuming that none or all of these patients would have developed distant metastases, respectively.

Impact of interpretative criteria

With observers blinded to the alternative modality and clinical outcome, all ^{18}F FDG-PET scans and CT scans were retrospectively scored using a five point ordinal scale to evaluate whether a more differentiated classification system might improve test accuracy, and to identify the most effective screening using the combined results. In all patients (with or without synchronous second primary tumour) every lesion was scored for suspiciousness of distant metastases using a five point ordinal Likert-scale (1=definitively benign, 2=probably benign, 3=equivocal, 4=probably malignant, 5=definitely malignant). In case of discrepancies between the scoring of the two screening modalities combined reading of CT and ^{18}F FDG-PET with visual correlation was performed by a nuclear physician and a radiologist and scored in consensus.

Statistical analysis

Sensitivity, specificity and accuracy of CT and ^{18}F FDG-PET were calculated. Receiver operated characteristics (ROC) analysis and areas under the ROC-curve were used as objective measures to evaluate the overall accuracy of CT, ^{18}F FDG-PET and both modalities combined (visually correlated) and the level of significance as well as the Q-point (Highest sensitivity/specificity) was calculated. Logistic regression analysis was performed to determine which diagnostic technique has the most impact on outcome. Confidence intervals were calculated with Confidence Interval Analysis 2.0 (Univ. of Southampton, 2000).

Results

Pretreatment screening identified distant metastases in 19 patients (21%; 95% confidence interval (CI) 15–28%) and second primary tumours in 6 (7%; 95% CI 3–12%). All patients with distant metastases were treated palliatively. Three of the six patients with a second primary tumour had disseminated lung cancer (lung and/or brain metastases) and they were also treated palliatively. The other three appeared to have limited stage

disease of their secondary primary and were treated with curative intent for either primary. In 38 of the total group of 92 patients (41%; 95% CI 33 – 50%) distant metastases (n=30; 33%; 95% CI 25 – 41%) or a second primary tumour (n= 8; 9%; 95% CI 5 – 15%) were detected during screening or within 12 months follow-up after screening.

Chest CT

At screening in clinical practice, chest CT was reported positive in 18/92 (20%) patients. Fifteen of them had distant metastases (n=11) or a synchronous second primary tumour (n=4). Three patients had false positive findings. Twenty-three of the 74 (31%) patients with a negative CT-scan at screening developed distant metastases (n=19; 26%) or a second primary tumour (n=4; 5%) within the 12 months follow-up (Table 1a and 1b). Three of the patients in which a second primary tumour was detected during screening had disseminated disease also. Since it is impossible to know whether these distant metastases developed from the primary or the second primary tumour these patients were left out of the accuracy calculation. The remaining 5 patients with second primary tumours (without disseminated disease) were used in the accuracy calculation and scored negative in screening for distant metastases. Hence, the total number of patients was 89. For the detection of distant metastases using CT the sensitivity was 37% and the specificity was 95% (Table 2a).

Table 1a. CT/PET combined results

PET	n = 89		M+	M-	Total
Positive	CT	pos	10	1	11
		neg	9	3	12
	Total		19	4	23
Negative	CT	pos	3	2	5
		neg	13	48	61
	Total		16	50	66

PET and CT findings compared with definitive outcome in the detection of distant metastases in a total number of 89 patients; M- = No distant metastases; M+ = Distant metastases

Table 1b. CT/PET combined results

PET	n = 92		M+	M-	Total
Positive	CT	pos	12	1	13
		neg	10	3	13
	Total		22	4	26
Negative	CT	pos	3	2	5
		neg	13	48	61
	Total		16	50	66

PET and CT findings compared with definitive outcome in the detection of distant metastases and synchronous primary tumours in a total number of 92 patients; M- = No distant metastases or second primary tumour; M+ = Distant metastases or second primary tumour positive

Table 2a. Accuracy of CT, PET, both CT and PET in the detection of distant metastases.

Method	Sensitivity	Specificity	PPV	NPV	Accuracy
n=89	percentage with 95% confidence interval				
CT	37 (24 - 52)	95 (88 - 98)	79 (57 - 91)	75 (66 - 82)	75 (67 - 82)
PET	53 (39 - 67)	93 (86 - 97)	80 (62 - 91)	80 (71 - 86)	80 (72 - 86)
PET and CT	63 (48 - 76)	95 (88 - 98)	86 (70 - 94)	84 (75 - 90)	84 (77 - 90)

PPV: positive predictive value; NPV: negative predictive value

¹⁸FDG-PET

At screening in clinical practice, ¹⁸FDG-PET was considered positive in 26/92 (28%) patients. Twenty-two had confirmed distant metastases (n=16, 17%) or a synchronous second primary tumour (n=6, 7%). Four ¹⁸FDG-PET studies were categorized as false-positive: two foci were localized in the abdomen and the other two in the chest. Sixteen of the 66 (17%) patients with negative PET at screening developed distant metastases (n=14, 15%) or a second primary tumour (n=2; 2%) within the 12 months follow-up (Table 1a and 1b). Compared to CT, PET had a higher sensitivity, with a slightly higher negative predictive value and accuracy (Table 2a).

CT and PET combined

The combination of CT and ¹⁸FDG-PET in the clinical practice setting are shown in Table 1b. In the total group of 92 patients, 31 (34%) patients had either a positive CT or positive ¹⁸FDG-PET. Thirteen (42%) of these 31 patients had both a positive chest CT as well as a positive ¹⁸FDG-PET, and malignancy was documented in 12 (8 distant metastases and 4 second primary tumours). The remaining patient had a lesion which disappeared at follow-up chest CT. Of the 18 patients with discrepant CT and PET findings, 5 (28%) had a positive CT and a negative ¹⁸FDG-PET: metastases were confirmed in three. Alternatively, in 10 of the 13 patients with a positive ¹⁸FDG-PET and a negative CT distant metastases (8) or a second primary tumour (2) were confirmed: in 4 patients ¹⁸FDG-PET detected a suspicious lesion, which after revision was also found on CT (lesions were initially considered benign (false negative) on CT alone). In 1 patient, ¹⁸FDG-PET detected a pulmonary lesion, which could not be found on CT after revision, but was confirmed at autopsy. In 2 patients, ¹⁸FDG-PET detected liver metastases, which were confirmed by dedicated CT or ultrasound. In 1 patient lumbar spine metastasis (confirmed by MRI) and in another patient a histologically confirmed intestinal malignancy was detected by PET. One patient had a lesion in the esophagus which was histologically confirmed. Thirteen (18% (13/73) patients developed distant metastases (n=11) or a second primary tumour (n=2) within the period of 12 months follow-up, despite an initially negative CT and ¹⁸FDG-PET. The results of combined (side-by-side visually correlated) reading of CT and ¹⁸FDG-PET in case of discrepancies are shown in Table 3. Accuracy data for CT combined with ¹⁸FDG-PET show a higher sensitivity with a minor increase in positive predictive value, negative predictive value and accuracy compared to CT and PET alone. (Table 2a).

Second primary tumours

In 6 of the 92 (7%) patients, a second primary tumour was found during initial screening while 2 of the 92 (2%) patients developed a second primary tumour during follow-up. In 4 of the 6 patients both ^{18}F FDG-PET and CT were true positive for a bronchogenic carcinoma. In the other 2 patients, ^{18}F FDG-PET was true positive while CT was false negative. One patient had a second primary tumour in the esophagus which was positive on PET but was missed on CT and was confirmed histologically. One patient had a bronchogenic carcinoma which was positive on ^{18}F FDG-PET but negative on CT. Although the lesion was seen on chest CT, it was initially considered to be benign but was confirmed during follow-up with a chest CT. The accuracy data for distant metastases and second primary tumours combined are shown in Table 2b. The group of second primary tumours alone was too small for statistical analysis.

Table 2b. Accuracy of CT, PET, both CT and PET in the detection of distant metastases and synchronous second primary tumors

Method	Sensitivity	Specificity	PPV	NPV	Accuracy
n=92	percentage with 95% confidence interval				
CT	39 (28 - 53)	94 (87 - 98)	83 (65 - 93)	69 (60 - 77)	72 (63 - 79)
PET	58 (45 - 70)	93 (84 - 97)	85 (70 - 93)	76 (66 - 83)	78 (70 - 84)
PET and CT	66 (52 - 77)	94 (87 - 98)	89 (76 - 96)	80 (70 - 87)	83 (75 - 88)

PPV: positive predictive value; NPV: negative predictive value

Scenario analyses

^{18}F FDG-PET was true-positive in 17 of the 24 (71%) patients with distant metastases in the chest, while chest CT detected a lesion in 15 of 24 (63%) patients. When only patients with locoregional control (80 patients out of 92 had locoregional control) during follow-up were analyzed, the sensitivity to detect distant metastases increased from 53% to 68% with ^{18}F FDG-PET, from 37% to 50% with CT and from 63% to 82% with ^{18}F FDG-PET and CT combined (Table 2c).

Table 2c. Accuracy of CT, PET, both CT and PET in the detection of distant metastases patients with locoregional control

Method	Sensitivity	Specificity	PPV	NPV	Accuracy
n=80	percentage with 95% confidence interval				
CT	50 (33 - 67)	95 (88 - 98)	79 (57 - 91)	83 (75 - 90)	83 (74 - 88)
PET	68 (51 - 82)	93 (86 - 97)	79 (61 - 90)	89 (80 - 94)	86 (79 - 91)
PET and CT	82 (65 - 92)	95 (88 - 98)	86 (69 - 94)	93 (86 - 97)	91 (85 - 95)

PPV: positive predictive value; NPV: negative predictive value

Table 3. Discrepancies between CT and PET reading

Patient	CT Score* [Site]	PET Score* [Site]	Coreading	Distant metastasis in FU	Confirmed by	Therapy for HNSCC	Status at 12 months
1	2, Lung	4, Lung	Atelectasis with inflammation	Yes	FU chest CT	Surgery	DOD
2	negative	5, Lumbar Spine	Lumbar spine not on CT	Confirmed at presentation	MRI	None	DOD
3	negative	4, Lung	Inflammatory lesion	Yes	Obduction	Curative radiotherapy	DOD
4	negative	4, Lung	Lesion confirmed, revision CT	Confirmed at presentation	Revision CT	Surgery	Alive
5	negative	4, Liver	Part of liver not on CT	Confirmed at presentation	CT-abdomen	Chemotherapy	DOD
6	negative	4, Intestine	Intestine not on CT	Confirmed at presentation	Biopsy	Palliative radiotherapy	DOD
7	negative	5, Liver	Not on CT	Confirmed at presentation	Ultrasound	Chemoradiation	DOD
8	negative	4, Axillary node	Seen on CT after revision	Confirmed at presentation	Revision CT	None	DOD
9	negative	4, Intestine	Not on CT	No (adenoma)	Autopsy	Surgery	Alive
10	negative	3, Pelvis	Not on CT	No	CT-abdomen	Surgery	Alive
11	2, Lung	4, Lung	Inflammatory lesion	No	Revision CT	Curative radiotherapy	Alive
12	4, Lung	2, Lung	Multiple small metastases	Confirmed at presentation	Revision CT	Palliative radiotherapy	DOD
13	4, Lung	2, Colon	Multiple small metastases	Confirmed at presentation	Biopsy	None	DOD
14	4, Lung	1, Pelvis	One small metastasis	Confirmed at presentation	Revision CT	Palliative radiotherapy	DOD
15	4, Lung	No lesion found	Small lesion (no growth)	No	FU chest CT	Surgery	Alive
16	4, Lung	3, Lung	Small lesion (no growth)	No	FU chest CT	Chemoradiation	Alive
17	negative	4, Esophagus	Missed on CT	second primary confirmed	Biopsy	Surgery	Alive
18	2, Lung	5, Lung	Inflammatory lesion	second primary confirmed	FU chest CT	Palliative radiotherapy	DOD

FU: follow-up; DOD: dead of disease

- ★ Likert 1 = definitively benign lesion
 2 = probably benign lesion
 3 = equivocal lesion
 4 = probably malignant lesion
 5 = definitively malignant lesion

In the 19 patients who could not be classified due to death or loss to follow-up before the end of the 12 months follow-up without development of distant metastases all ^{18}F FDG-PET and CT-scans were negative at initial screening. If all would have developed distant metastases within 12 months (worst case scenario), the sensitivity of CT, PET and CT and PET combined would be 22%, 33% and 39%, respectively, with specificities of 95%, 93% and 95%, respectively. Alternatively, the best case scenario (no patient developing metastases) revealed sensitivities of 37%, 53%, 63%, at specificities of 96%, 95% and 96% for CT, PET and combined CT and PET reading, respectively.

Refined interpretation criteria

The scorings of all scans according to the five point ordinal scale and presence or absence of distant metastases are shown in Table 4. If in one patient more lesions were scored, the lesion with the highest score was used for statistical analysis. Three patients in which a second primary tumour but no distant metastases were detected scored negative (Likert = 0) with respect to the screening for distant metastases. The prevalence of scores for PET and CT were: no lesion: 65 and 62%, score 1: 2 and 4%, score 2: 5 and 9%, score 3: 4 and 11%, score 4: 16% and 11%, and score 5: 8 and 5%, respectively.

Table 4. The highest ordinal scores* for lesions in the detection of distant metastases by PET and CT.

PET score*	CT score*	Distant metastasis		
		Yes	No	Total
0	0	6	40	46
0	1	0	3	3
0	2	1	2	3
0	3	1	6	7
0	4	0	1	1
1	4	1	0	1
2	0	1	0	1
2	2	1	1	2
2	4	2	0	2
3	0	1	1	2
3	3	0	1	1
3	4	0	1	1
4	0	5	1	6
4	2	1	1	2
4	4	3	1	4
4	5	3	0	3
5	0	2	0	2
5	2	1	0	1
5	4	1	0	1
5	5	3	0	3
Total		33	59	92

0 = no lesion; 1 = definitively benign lesion; 2 = probably benign lesion; 3 = equivocal lesion; 4 = probably malignant lesion; 5 = definitively malignant lesion

ROC analyses provided areas under the curve (AUCs) of 0.673 and 0.837 for CT and PET (p=0.0074), respectively (both significantly different from the true AUC = 0.5 (Null hypothesis: true area 0.5; Figure 2). The Q-point for PET was found at a five point ordinal scale score =1 for a sensitivity of 74% and a specificity of 87%. For CT this point lies at a score =4 with a sensitivity of 39% and specificity of 94%. These findings imply that PET scores better in the detection of distant metastases or a second primary tumour than CT. The Q-point for PET at a five point ordinal scale score =1 suggests that if every lesion scored with PET is considered malignant the highest accuracy data are reached. For CT these numbers are reached if only lesions with the highest suspicion (score ≥ 4) are considered malignant.

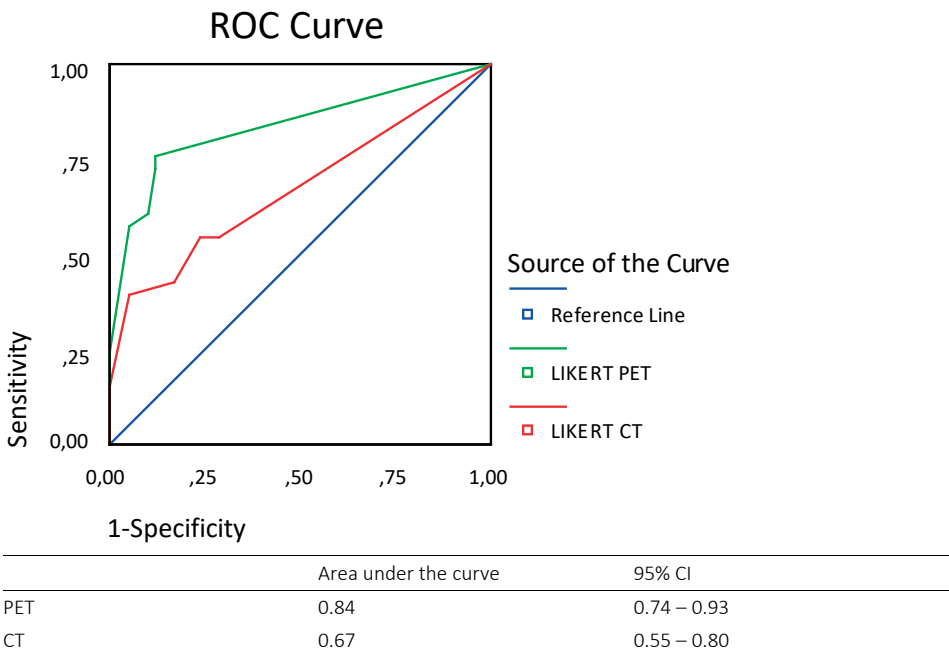


Figure 2. ROC analysis of five point ordinal classification system in reporting CT and PET results.

Logistic regression analysis was performed to identify a strategy for the best use of the five point ordinal scale. When PET and CT scores are analyzed at a cutoff point >1 in all 92 patients (lesion seen or not), PET has a significance of 0.001 as compared to 0.015 for CT. When PET is excluded the significance drops to 0.862. This suggests that PET predicts the presence of distant metastases better than CT. Secondly, regression analysis was performed in the 21 patients with a score >1 for PET as well as CT. In this scenario CT has a slightly higher significance of 0.089 as compared to 0.323 for PET. When CT is left out of the equation the significance drops to 0.520.

Regarding clinical relevance, the results of the Q-point combined with logistic regression analysis could imply the following conclusions: If a lesion is not seen on PET this patient has probably no distant metastases. If a lesion is scored positive (even low suspicion i.e. score of 1 or 2) on PET and negative on CT, it is still highly probable that this lesion is malignant. In patients with both a positive PET and CT, the prediction of distant metastases is most likely if CT score is >4.

Discussion

In the present study, in 21% (19/92) of the patients distant metastases were detected during screening at initial presentation. In 16 of the 30 patients with distant metastases (at evaluation or follow-up), these lesions were detected by ^{18}F FDG-PET only and in 11 of the 30 patients by chest CT only. ^{18}F FDG-PET had a higher sensitivity (53% vs. 37%) and negative predictive value (80% vs. 75%) than CT alone as screening modality for distant metastases. The combination of CT and ^{18}F FDG-PET had the highest sensitivity (63%).

Results of imaging techniques are usually not dichotomous, but comprise a spectrum of probabilities. Therefore, we investigated the relative performance of ^{18}F FDG-PET and CT also as a function of the level of the observers' confidence. In ^{18}F FDG-PET reading only scans with probably or definitely malignant lesions have to be considered positive, whereas scans with only probably or definitely benign or equivocal lesions have to be considered negative. When a lesion is seen with both modalities, CT scoring adds information to final outcome; probably or definitely malignant lesions are to be considered malignant, whereas definitively, probably benign or equivocal lesions are to be considered negative. The value of ^{18}F FDG-PET appeared to be higher than the value of CT, although CT remains important as screening modality.

This study focused on detection of distant metastases because of their impact on treatment planning with an emphasis on detection of the highest number of true-positive events in combination with lowest number of false-positive findings. In HNSCC patients, a low number of false-positive findings outweighs high false-negative findings. A patient with false-positive screening will incorrectly be denied treatment with curative intent, whereas a patient with false-negative screening will incorrectly undergo futile extensive treatment. In general, ^{18}F FDG-PET findings have to be confirmed by conventional diagnostic techniques. Therefore, in false-positive ^{18}F FDG-PET findings the risk of incorrectly withheld of treatment is negligible, but these findings may induce additional costly examinations. Therefore, a cost-effectiveness is warranted to investigate if the costs of the avoided futile extensive treatments outweighs the costs of ^{18}F FDG-PET and additional examinations.

In screening for distant metastases, synchronous second primary tumours can occasionally be detected. Second primary tumours also have impact on survival and may alter the therapeutic management in HNSCC patients. Synchronous second primary tumours

are diagnosed in approximately 4% of the HNSCC patients. Although the head and neck region is the most frequent site, synchronous primary tumours also occur below the clavicles: lungs, esophagus and other sites.[13] On CT, differentiation between a solitary pulmonary metastases and a second primary bronchiogenic carcinoma may be difficult. Therefore, most studies report on intrathoracic malignancies without separating metastases from primary tumours. Nishiyama et al.[14], found synchronous primary tumours in 5 of 53 (9%) of previously untreated head and neck cancer patients using ^{18}F FDG-PET. We identified a second primary tumour during screening in 7% (6/92) of the patients while an additional 2% (2/92) of the patients developed a second primary tumour during follow-up. CT detected 4 of 6 (67%) and ^{18}F FDG-PET 6 of 6 (100%) second primary tumours which were identified during screening.

Locoregional control of HNSCC is an important prognostic factor for the development of distant metastases. Therefore, if locoregional recurrence occurs during follow-up before distant metastases become manifest it is not clear if occult metastases were already present during initial screening or tumour spread from locoregional recurrence resulted in the development of distant metastases. If corrected for locoregional control the sensitivity of screening with CT and ^{18}F FDG-PET increases significantly to 82%. This would more likely reflect the real value of detection at initial screening.

Because of the high incidence of lung metastases and the frequent combination of distant metastases at other sites with lung metastases, examination of the chest is most important in screening for distant metastases. In the present study in 26% (24/92) of all the patients and in 80% (24/30) of the patients with distant metastases lung metastases were found, while 8% (7/92) of the patients had a second primary tumour in the chest. However, distant metastases may also develop outside the chest. The fact that ^{18}F FDG-PET screens not only the chest but the whole body biased the comparison of ^{18}F FDG-PET and CT. When corrected for localization in the thorax ^{18}F FDG-PET detected 7% (17/31 versus 15/31) more lesions as compared to CT. This implies that even in pulmonary lesions ^{18}F FDG-PET has an added value over CT.

Most studies on screening for distant metastases in HNSCC patients using CT scan of the chest identified a substantial percentage of patients with distant metastases and second primary tumours.[3,10,15-20] Some other studies report a very low percentage of distant metastases using CT during screening.[21-24] In all these studies no clear follow-up data with a final assessment of the development of distant metastases or second primary tumours were mentioned. Because these data are lacking in all studies, especially in patients initially negative on screening, the accuracy of chest CT cannot be determined. Moreover, due to the variation in inclusion criteria, a straightforward meta-analysis is not possible. Recently, a retrospective study on the value of screening using chest CT with an adequate follow-up has been performed in 109 HNSCC patients with risk factors. If positive findings on screening and a follow-up of at least 12 months is used as reference standard in HNSCC patients with locoregional control, the sensitivity of the CT scan of the chest was 73% (CI 95%; 59 – 83%) with a specificity of 86% (CI 95%; 78 – 91%).[2] In the

present prospective study these figures are 50% (CI 95%; 33 – 67%) and 95% (CI 95%; 88 – 98%), respectively.

Some studies report on the detection of distant metastases by ^{18}F FDG-PET.[25-30] Because the patient groups in these studies are very heterogeneous and different from each other regarding tumour types, tumour stage and follow-up no reliable accuracy data can be calculated. In reviews, Vermeersch et al.[31] and Goerres et al.[32] also concluded that due to the wide variation in methodology and the lack of information in available literature, a straightforward meta-analysis of ^{18}F FDG-PET literature or a probability analysis on the detection of distant metastases could not be conducted. Only in the small series of 12 patients by Teknos et al.[25], ^{18}F FDG-PET was compared to the standard conventional diagnostic technique, e.g. CT-scan of the chest. In the present study, the values of ^{18}F FDG-PET and CT are compared in a well-defined group of substantial size. Kim et al.[33] evaluated the ability of combined ^{18}F FDG-PET/CT to detect second primary tumours and distant metastases in a large number of head and neck cancer patients and concluded that it was a useful method. However, the group was heterogeneous regarding tumour type, site and stage and the minimal follow-up was short. In only 5% of the 349 head and neck cancer patients distant metastases were detected during initial staging.

Although ^{18}F FDG-PET detects distant metastases more frequently, CT may detect distant metastases below detection limit of ^{18}F FDG-PET (i.e. <4 mm). Conversely, ^{18}F FDG-PET may detect distant metastases which can only be confirmed by CT and obviously also extra distant metastases outside the chest area. If CT and ^{18}F FDG-PET are both positive, distant metastasis are very likely to be present. Histopathology should be used to confirm these distant metastases whenever feasible. When CT is positive and ^{18}F FDG-PET is negative, the final assessment of combined reading depends on the size of the lesion on CT: in case of small lesions below detection limit of ^{18}F FDG-PET, outcome is predicted by CT. In larger lesions ^{18}F FDG-PET adds extra information and these lesions can be considered benign. When CT is negative and ^{18}F FDG-PET is positive, the final assessment of combined reading depends on localization. In pulmonary lesions, ^{18}F FDG-PET adds information and these lesions should be considered malignant. Moreover, in most cases, CT does indicate these lesions at revision. Lesions found by ^{18}F FDG-PET outside scanning range should be confirmed with appropriate diagnostic methods. Therefore, screening with both modalities should be performed using abovementioned strategy based on the scoring on the five point ordinal Likert-scale and the detection limit of ^{18}F FDG-PET. Currently, PET/CT is frequently used for radiation treatment planning (34). In patients planned for radiotherapy extending the scanning area to the whole body and using state of the art CT scanning protocol is easily performed with limited additional costs.

In conclusion, ^{18}F FDG-PET is a valuable diagnostic tool in screening for distant metastases in HNSCC patients with high risk factors. Screening with a combination of CT-scan of the thorax and whole body ^{18}F FDG-PET decreases over-treatment. It results in a reduction of futile mostly extensive treatments in these patients.

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Chapter 3

Chest CT and Whole body ^{18}F FDG-PET are cost-effective in screening for distant metastases in head and neck cancer patients

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Abstract

The aim of the study was to define the cost-effectiveness of whole body ^{18}F FDG-PET, as compared with chest CT, in screening for distant metastases in patients with head and neck squamous cell carcinoma (HNSCC). In a multi-center prospective study, 145 consecutive patients with high risk factors for distant metastases and scheduled for extensive treatment underwent chest CT and whole body ^{18}F FDG-PET for screening for distant metastases. The cost data of 80 patients in whom distant metastases developed or who had a follow-up of at least 12 months were analyzed. Cost-effective analysis, including sensitivity analysis, was performed to compare the results of ^{18}F FDG-PET, CT and a combination of CT and ^{18}F FDG-PET (CT + ^{18}F FDG-PET). Pretreatment screening identified distant metastases in 21% of the patients. ^{18}F FDG-PET had a higher sensitivity (53% vs. 37%) and positive predictive value (80% vs. 75%) than CT. CT + ^{18}F FDG-PET had the highest sensitivity (63%). The average costs in the CT, ^{18}F FDG-PET and CT + ^{18}F FDG-PET groups amounted to €38,558 (~\$57,705), €38,355 (~\$57,402) and €37,954 (~\$56,801), respectively, in the first year of screening. CT + ^{18}F FDG-PET resulted in savings between €203 (~\$303) and €604 (~\$903). Sensitivity analysis showed that the dominance of CT + ^{18}F FDG-PET was robust. In HNSCC patients with risk factors, pretreatment screening for distant metastases by chest CT is improved by ^{18}F FDG-PET. The combination of ^{18}F FDG-PET with CT is the most effective, without leading to additional costs.

Introduction

Head and neck squamous cell carcinoma (HNSCC) accounts for approximately 5% of all malignant tumors worldwide. Early HNSCC can usually be managed successfully with either radiotherapy or surgery. However, two thirds of the patients with HNSCC present with advanced disease and are usually treated by a combination of surgery followed by chemotherapy or radiotherapy (1). Distant metastases usually occur late in the course of the disease. The lungs, bone and liver are the most frequent sites. The presence of distant metastases at initial evaluation influences the prognosis and the treatment choice. No effective systemic treatment for disseminated HNSCC is currently available; patients with distant metastases are generally not considered curable and often receive only palliative treatment. Overall survival for patients with distant metastases detected at initial screening is significantly poorer than for patients with distant metastases missed during initial screening and detected during follow-up (2). Therefore, screening for distant metastases is important to avoid futile and often extensive treatments.

The overall incidence of clinically identified distant metastases in HNSCC at presentation varies from 2 to 18% (2-5) and is generally considered too low to warrant routine screening for distant metastases in all HNSCC patients (3,6). The detection is directly related to the stage of disease, particularly to the presence and extension of lymph node metastases and locoregional control, and depends on the applied diagnostic methods (2,6-9). Therefore, staging or screening on distant metastases using the best available diagnostic techniques in patients with high risk factors is considered worthwhile (2,3,10).

As most distant metastases are located in the lung, chest CT is the most often used technique to detect distant metastases in HNSCC. However, with chest CT several distant metastases and primary tumours are still missed. Positron emission tomography (PET) with ^{18}F -fluorodeoxyglucose (^{18}F FDG) is able to detect tumor deposits in the whole body. ^{18}F FDG-PET detects more distant metastases than does CT, but the combination of both techniques, as currently provided with hybrid PET/CT scanners, appears to be superior (11,12).

^{18}F FDG-PET is a costly technique and there are various clinical applications. Therefore, there is a need to use it for the most valuable applications to have the most efficient use of resources. We have performed a prospective, multicenter clinical trial determining the potential added value of whole body ^{18}F FDG-PET in screening for distant metastases in HNSCC patients with risk factors to the best conventional imaging with CT. The clinical results are presented elsewhere (11). A prospective cost-effectiveness study was performed in close conjunction with the clinical trial to be able to assess the costs and benefits of ^{18}F FDG-PET in this patient group. We adopted a hospital perspective, in which only the direct costs of outpatient and inpatient diagnostic procedures and treatment are considered.

Materials and Methods

The multicenter study was carried out at 3 university medical centers in The Netherlands. Eligibility criteria were patients with HNSCC, candidates for extensive treatment with curative intent (surgery or radiotherapy with or without chemotherapy), and patients at increased risk for distant metastases (i.e.: ≥ 3 lymph node metastases ($n=20$), bilateral lymph node metastases ($n=36$), lymph node metastases of ≥ 6 cm ($n=30$), low jugular lymph node metastases ($n=6$), regional tumor recurrence ($n=10$) and second primary tumours ($n=25$), as assessed by palpation, CT, MRI, or ultrasound-guided fine-needle aspiration cytology (3). The protocol was approved by the Medical Ethical Committee of the VU University Medical Center and all patients gave written informed consent.

Imaging techniques

All patients underwent chest CT and ^{18}F FDG-PET, in random order as dictated by logistics. Spiral CT scans were obtained with a fourth-generation Siemens Somaton Plus (Siemens AG) after the intravenous administration of contrast medium (Ultravist, Schering AG). ^{18}F FDG-PET was performed after patients had fasted for 6 hours with ample access to water. At 60-90 minutes after the intravenous administration of 250-370 MBq ^{18}F FDG, the imaging of trajectory knee-skull base was performed using a dedicated full-ring bismuth germinate PET scanners (in Amsterdam/Groningen, ECAT HR + [CTI/Siemens]; in Nijmegen, CTI/Siemens ECAT EXACT [CTI/Siemens]). Any focal abnormality suggestive of malignancy was reported (11).

Data analysis

The result of the clinical diagnostic work-up between presentation and a follow-up of 12 months was used as reference standard, and patients were classified as positive or negative with respect to the presence of distant metastases. Follow-up was performed every 6 weeks in the first year and consisted of visits to the outpatient clinic. During follow-up, the dates of the detection of distant metastases, second primary tumours, or death were recorded. Although the primary goal was screening on distant metastases, second primary tumours were also registered.

Cost analysis

The hospital's perspective was considered. The cost analysis focused on direct medical costs. The base year was 2008. The costs of diagnosis and treatment were based on the total clinical consumption of all evaluable patients. For the most important items, unit costs were determined because these were a better estimator of the theoretic opportunity costs (13,14). These costs include not only the measurable costs of an intervention (e.g. radiotherapy, surgery, and imaging) but also the services that are not directly allocated to patient care, such as hospital overhead and administrative personnel. Therefore,

all hospital costs can be assigned to the interventions given in the hospital. For the determination of these unit costs the micro-costing approach was used (15).

Table 1 shows the most important unit costs used in this analysis. The costs of ¹⁸FDG-PET scanning, hospital days, outpatient visits, and day-care treatments are composed of variable and overhead costs. The variable costs consisted of manpower (e.g., doctors, nurses) and materials (e.g. medication, supportive patient care, meals). The overhead costs were related to general hospital services and housing. The costs of radiotherapy covered the entire process, including preparation. When patients were subjected to chemotherapy, the costs of the chemotherapeutic agent were derived from the Pharmaceutical Compass (16) and included in the cost analysis; costs of administration are covered by hospitalizations and day-care treatment (15). For most laboratory and diagnostic tests, the Dutch tariff system was used as an approximation of unit costs.

Table 1: Costs of hospital days, day care treatment, outpatient visits and FDG-PET scan (in 2008 Euros)

	Outpatient visit	Day care	Normal care	Intensive care	FDG-PET scan
Specialist	23	20	28	41	
Nursing and administration	24	43	185	667	97*
Materials		33	42	137	295
FDG					294
Housing	6	72	102	180	
Overhead	12	36	77	237	241
<i>Total</i>	<i>65</i>	<i>204</i>	<i>434</i>	<i>1,262</i>	<i>927</i>

* Includes specialist costs

Allocation of resource use and details of cost analysis

Data on resource utilization use were collected from the hospital information system, patient files and the case report forms. Data on the numbers of hospital days, outpatient visits, day-care treatments, diagnostic activities, laboratory testing, radiation therapy sessions, surgical procedures and medication were collected.

As in all clinical studies concerned with diagnostic techniques, there are several possible diagnostic outcomes; true-positive, false-positive, true-negative and false-negative. A positive test outcome (distant metastases and (incurable) second primary tumour) results in palliative treatment and a negative outcome (no distant metastases and (incurable) second primary tumour) results in curative treatment. In table 2, all different test outcomes and treatment possibilities together with the translation and consequence for the cost analysis are presented. However, for the clinical decision making toward either curative or palliative treatment, other aspects are also of interest; these should be incorporated in the cost analysis as well. These aspects relate to the general condition of the patient, the patient's preferences, the cost implications of the clinical approach, and the possible use of second-line diagnostics to confirm or reject an initial test outcome. In addition, ¹⁸FDG-PET has proven its value in previous studies, and it would, therefore, be

unethical to leave its test outcome out of the clinical decision. This decision to include ^{18}F FDG-PET resulted several additional test outcome treatment combinations that had to be adjusted for in the cost analysis to be able to judge the added value of ^{18}F FDG-PET in screening for distant metastasis and synchronous primary tumours in HNSCC patients.

Table 2: Test-treatment combination and consequence for cost analysis

Test-Treatment combination	Consequence	Data source
True positive → Curative treatment	Adjustment for overestimation of costs	Average of resource use for curative intervention from patient file
True positive → Palliative treatment	None	-
False positive → Curative treatment	Adjustment for overestimation of costs	Average of resource use for curative intervention from patient file
False positive → Palliative treatment	None	-
True negative → Curative treatment	None	-
True negative → Palliative treatment	Adjustment for underestimation of costs	Average of resource use for similar curative intervention
False negative → Curative treatment	None	-
False negative → Palliative treatment	Adjustment for underestimation of costs	Average of resource use for similar curative intervention

In the cost analysis, the following 3 diagnostic strategies are compared: CT alone, ^{18}F FDG-PET alone, and the combination of the 2 visually correlated. On the basis of the test outcomes and the aspects already mentioned, clinical experts determined the appropriateness of the clinical approach for each patient in the 3 diagnostic scenarios; subsequently the consequences for the cost analysis were determined. These consequences were based on resource use in patients undergoing comparable interventions and on information from clinical experts who indicated what resource use was incorrectly withheld or used based on clinical characteristics of the patients. This resource use includes the costs of hospitalization, operations, radiotherapy and revalidation and also includes the number of ancillary imaging techniques, hospitalizations, and interventions that would not have been applied in the absence of the ^{18}F FDG-PET scan. It was decided to exclude the impact on laboratory testing from the base case analysis because these are very patient-specific and independent of further treatment.

Sensitivity analysis

The estimation of resource use is associated with substantial uncertainty; because of patient variation, these are tested in multiple sensitivity analyses to determine the impact on the cost-effectiveness outcomes. Additionally, we performed a sensitivity analysis for

which we included an estimation of the costs of laboratory testing associated with hospitalization for extensive treatment that was futile or that should have been performed based on the diagnostic test outcome.

Results

Patient characteristics

One hundred and forty-five patients were entered in the study (11). After the exclusion of patients who were incorrectly included or had logistical problems, 111 patients remained. Because the reference standard for further data analysis was the detection of distant metastases or negative follow-up of 12 months, we excluded 19 patients who died without distant metastases within these 12 months follow-up. Therefore, we obtained evaluable data for 92 patients. For the cost-effectiveness analysis the complete data for 80 patients were available. Of these 80 patients, 63 were men, and the mean age was 60 years (range 40 - 81). Primary tumour sites were the oral cavity (n=17), oropharynx (n=24), hypopharynx (n=16), larynx (n=14), cervical esophagus (n=3) and lymph node metastases of an unknown primary tumour (n=18). Ten patients had more than 1 synchronous primary tumor. The patient characteristics in this study were comparable with the patient characteristics included in the clinical study.

Clinical study

Pretreatment screening identified distant metastases in 17 of 80 patients (21%; 95% confidence interval [CI], 15–28%) and second primary tumours in 6 of 80 patients (7%; 95% CI, 3–12%). All patients with distant metastases were treated palliatively. Half of the patients with a second primary tumour had disseminated lung cancer (lung or brain metastases), and they also received palliative treatment. The other 3 patients appeared to have limited-stage disease of their secondary primary and were treated with curative intent for both primary tumours. In 32 of 80 of the total group of patients (41%, 95%CI 33 – 50%) distant metastasis (33%; 95% CI 25 – 41%) or a second primary tumour (9%; 95% CI 5 – 15%) were detected during screening or within 12 months follow-up.

¹⁸FDG-PET had a higher sensitivity (53% vs. 37%) and positive predictive value (80% vs. 75%) than did chest CT. The combination of CT and ¹⁸FDG-PET had the highest sensitivity (63%).

Details of the clinical study are presented elsewhere (11).

Cost analysis

The distribution of test outcomes and treatment options are presented in Table 3. From this table, it appears that in the CT only-scenario 11.25% of the patients were not treated in accordance with the test outcome. However, in 2.50% of these patients the positive

test outcome related to an operable second primary, and therefore the curative operations were appropriate. In another 2.50% a palliative approach was chosen, despite a negative test outcome because of patient preference or clinical condition. As a consequence 6.25% of these patients remained for whom a correction must be made for inappropriately withheld (3.75%) or given curative treatment (2.5%).

Table 3: Distribution of patients over test outcome and treatment approach

		CT	FDG-PET	FDG-PET + CT
Diagnostic test	True positive	Curative treatment	0,0375	0,0875
		Palliative treatment	0,1500	0,1625
	False positive	Curative treatment	0,0125	0,0250
		Palliative treatment	0,0125	0,0000
	True negative	Curative treatment	0,5250	0,5125
		Palliative treatment	0,0000	0,0125
	False negative	Curative treatment	0,2000	0,1500
		Palliative treatment	0,0625	0,0500

In the ¹⁸FDG-PET only scenario, 16.25% of the patients were not treated according to their test outcome. Of these patients, 14% were curatively treated for an operable second primary tumour, and 7% were treated palliatively despite a negative test because of the patient's condition. In another 7% of these patients, the ¹⁸FDG-PET result raised questions that were answered with additional diagnostic testing; the ¹⁸FDG-PET was, therefore, considered to be false-positive but this did not influence the treatment decision. Finally, 5% of the patients with a false-negative test outcome were treated palliatively; this had no impact on the cost analysis because the clinicians indicated there would have been no difference in curative and palliative treatments. Thus, 11.25% of the patients remained for whom a correction must be made for inappropriately withheld or given curative treatment.

In the third scenario, the combination of CT and ¹⁸FDG-PET, 13.75% received a treatment that was not in line with the test outcome. Of these patients 16.75% were curatively treated for an operable second primary tumour and 8.25% were treated palliatively, despite a negative test result because of the patient's condition. This scenario also included a patient for whom the ¹⁸FDG-PET result raised questions (these questions were solved with additional diagnostic testing) and a patient for which the clinicians indicated that there was no difference in resource use between palliative and curative treatments. This scenario resulted in an adjustment for inappropriate resource use of the patients who were treated curatively despite a positive test outcome.

In 3 patients, the ¹⁸FDG-PET scan resulted in ancillary imaging or hospitalizations and interventions that would not have been applied in the absence of the ¹⁸FDG-PET scan; these resources were also defined and subtracted from the total resource use in the CT-

only scenario. The results of the cost analysis for all diagnostic strategies are presented in table 4. In this table, the difference in costs between treatment strategies and study-related diagnostic procedures (CT and ¹⁸FDG-PET) were included. A curative treatment costs approximately €41,369 and a palliative treatment €26,328.

Table 4: Resource use and average costs per patients for the three scenarios

			CT	FDG-PET	FDG-PET+CT	CT	FDG-PET	FDG-PET+CT
Curative	Hospital days	14667	0.7875	0.725	0.6875	11550	10634	10084
	Day care	124	0.7875	0.725	0.6875	98	90	85
	Consults	1575	0.7875	0.725	0.6875	1240	1142	1083
	Surgery	10388	0.7875	0.725	0.6875	8181	7531	7142
	Radiother	5074	0.7875	0.725	0.6875	3995	3678	3488
	Chemo	1243	0.7875	0.725	0.6875	979	901	855
	Imaging							
	FDG-PET	0	0.7875	0.725	0.6875	0	927	927
	CT	0	0.7875	0.725	0.6875	173	0	173
	Other	2626	0.7875	0.725	0.6875	2068	1904	1805
	Other diagnost	5942	0.7875	0.725	0.6875	4679	4308	4085
	Total	41639	0.7875	0.725	0.6875	32963	31115	29727
Palliative	Hospital days	7678	0.2125	0.275	0.3125	1632	2111	2399
	Day care	124	0.2125	0.275	0.3125	26	34	39
	Consults	1575	0.2125	0.275	0.3125	335	433	492
	Surgery	1359	0.2125	0.275	0.3125	289	374	425
	Radiother	4418	0.2125	0.275	0.3125	939	1215	1381
	Chemo	2606	0.2125	0.275	0.3125	554	717	814
	Imaging							
	FDG-PET	0	0.2125	0.275	0.3125	0	927	927
	CT	0	0.2125	0.275	0.3125	173	0	173
	Other	2626	0.2125	0.275	0.3125	558	722	821
	Other diagnost	5942	0.2125	0.275	0.3125	1263	1634	1857
	Total	26328	0.2125	0.275	0.3125	5768	8167	9328
Total	Hospital days					13182	12745	12483
	Day care					124	124	124
	Consults					1575	1575	1575
	Surgery					8469	7905	7566
	Radiother					4934	4893	4869
	Chemo					1533	1618	1669
	Imaging							
	FDG-PET					0	927	927
	CT					173	0	173
	Other					2626	2626	2626
	Other diagnost					5942	5942	5942
	Total					38558	38355	37954

Comparing the diagnostic strategies, the most important changes are seen in the costs of hospital days, surgery and radiotherapy. These changes are caused by the reduction of futile operations and curative radiotherapy in both the ¹⁸FDG-PET and CT + ¹⁸FDG-PET scenario versus the CT scenario.

These reductions countered the introduction of additional diagnostic costs by ^{18}F FDG-PET testing and resulted in an average cost per patient of €38,558 in the CT only-scenario, €38,355 in the ^{18}F FDG-PET only-scenario and €37,954 in the CT + ^{18}F FDG-PET scenario. The differences between the different scenarios are small, the introduction of ^{18}F FDG-PET led to a cost reduction between €203 and €604.

Sensitivity analysis

The costs of hospitalizations, operations, radiotherapy and diagnostic imaging are the main cost drivers in this patient population. The results of several sensitivity analyses on these main cost drivers are presented in Table 5.

The cost differences now ranged between €110 and €697. Variation in resource use and costs affected the differences between the strategies. Furthermore, the results still remained robust in favor of the CT + ^{18}F FDG-PET scenario.

Table 5: Results of the sensitivity analysis

Sensitivity analyses	Difference				
	CT	FDG-PET	FDG-PET + CT	FDG-PET vs CT	FDG-PET + CT vs CT
Costs hospital days 10% higher	39876	39630	39202	-247	-674
Costs hospital days 10% lower	37240	37081	36706	-159	-534
Costs of PET 10% higher	38558	38448	38047	-110	-511
Costs of PET 10% lower	38558	38263	37861	-296	-697
Costs of surgery 10% higher	39405	39146	38711	-259	-694
Costs of surgery 10% lower	37711	37565	37197	-146	-514

Discussion

We presented the results of the cost and cost effectiveness analysis for 3 diagnostic strategies in screening for distant metastasis and synchronous primary tumours in HNSCC patients. We showed that ^{18}F FDG-PET with or without CT was a valuable diagnostic tool in these patients; its addition results both in a reduction of futile operations and an increase in appropriate curative interventions, without leading to additional costs. There are a few aspects of the cost analysis that deserve some attention.

Although the cost estimates are sensitive to changes in the main cost drivers in these patients, the differences remain small. Furthermore, it is not likely that these variations will lead to a cost increase with the introduction of ^{18}F FDG-PET because we estimated the savings associated with the reduction in futile operations conservatively. We, for instance, did not include the laboratory and pathology costs associated with the prevented operations and hospitalizations.

During the last decade, the costs for radiotherapy in HNSCC have increased due to implementation 3-dimensional conformal radiotherapy, intensity-modulated radiation techniques, stereotactic radiotherapy and combination with chemotherapy (17,18). The introduction of these techniques implies that the savings with ^{18}F FDG-PET could be higher.

Additionally, there is 1 difference between the cost and the clinical analysis. One patient had a lesion in the liver that would have been missed on a conventional CT-thorax. However, the result for this patient was scored positive due to extension of the scanning range to the abdomen. The results for this patient were scored true-positive for the cost analysis and scored false-negative for the clinical study. This, again, was a conservative estimation because an adjustment for the underestimation of resource use in this patient based on its test outcome was not necessary. Thereby the difference between the ^{18}F FDG-PET and CT scenario was underestimated.

Previous studies in fewer patients with advanced head and neck cancer also found that savings from futile extensive operations exceed the costs of ^{18}F FDG-PET (2,18). This study replicates these findings in a much larger number of patients. Additionally, we were able to demonstrate the effect of combining the test results of independently performed ^{18}F FDG-PET and CT tests. It is likely that integrated ^{18}F FDG-PET and CT imaging will further improve efficiency (19).

Generalization of the results to other countries is not straightforward because health-care organization and prices differ. However, the outcomes of this study mainly depend on the sensitivity and specificity of ^{18}F FDG-PET \pm CT and the costs of ^{18}F FDG-PET \pm CT. Especially the prices of ^{18}F FDG-PET and hospital days could differ between countries. In general, these cost prices are higher in other countries, especially in the United States. In the sensitivity analysis, the higher cost prices of ^{18}F FDG-PET still result in savings (with thresholds of €1,130 for the ^{18}F FDG-PET and €1,530 for the ^{18}F FDG-PET + CT scenarios). The higher prices of hospital days always result in savings in the ^{18}F FDG-PET scenarios. The most important value of ^{18}F FDG-PET lies in offering patients a better (and more efficient) diagnostic strategy.

Conclusion

^{18}F FDG-PET is a valuable diagnostic tool when screening for distant metastasis and synchronous primary tumours in HNSCC patients. The use of ^{18}F FDG-PET results in both a reduction of futile operations and an increase in appropriate curative interventions in these patients, without leading to additional costs.

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Chapter 4

Interobserver Variability in Chest CT and Whole Body FDG-PET Screening for Distant metastases in Head and Neck Cancer Patients

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Abstract

The aim of the study was to assess the interobserver variability in chest computed tomography (CT) and whole body ^{18}F FDG-PET screening for distant metastases in head and neck squamous cell carcinoma (HNSCC) patients. Chest CT and whole body ^{18}F FDG-PET of 69 patients with high risk factors who underwent screening for distant metastases were analyzed. All scans were independently read by two experienced radiologists or nuclear physicians who were blinded to the other examinations and follow-up results. A kappa of 0.516 was found for assessment of size on CT. Kappa values for origin and susceptibility of 0.406 and 0.512 for CT and 0.834 and 0.939 for ^{18}F FDG-PET were found, respectively. The overall conclusions had a kappa of 0.517-0.634 for CT and 0.820-1.000 for ^{18}F FDG-PET. In screening for distant metastases in HNSCC patients with high risk factors, chest CT readings had a reasonable to substantial agreement, while ^{18}F FDG-PET readings showed an almost perfect agreement. These findings suggest that for optimal assessment in clinical practice, ^{18}F FDG-PET most often can be scored by one observer, but CT should probably more often be scored by different observers in consensus or combined with ^{18}F FDG-PET.

Introduction

Head and neck squamous cell carcinomas (HNSCC) grow locally invasive and have a proclivity to metastasize to regional lymph nodes rather than to spread hematogenously. However, the presence of distant metastases influences prognosis and choice of treatment in patients with HNSCC. Patients with HNSCC and distant metastases are generally not considered curable and are treated mostly palliative.

In both clinical and autopsy studies, the lungs are the most frequent site of distant metastases in patients with head and neck cancer (1-3). Moreover, lung metastases occur in 61-91% in combination with distant metastases at other sites. Distant metastases at other sites without simultaneous lung metastases are found in only 6-25% (2). Because of the high incidence of lung metastases and the frequent combination of distant metastases at other sites, examination of the thorax is most important in screening for distant metastases.

The diligence with which technique the lungs should be screened remains controversial. Computed tomography (CT) is more sensitive in the detection of pulmonary nodules than plain chest radiography, because of the superiority of CT in detecting small nodules (1,4,5).

In a previous study, it was concluded that chest CT was the single most important diagnostic technique for pretreatment screening for distant metastases (1). However, despite negative screening by chest CT and locoregional tumour control some patients develop distant metastases (6). These distant metastases must have been present at diagnostic work-up, but were apparently below the detection limit of screening tests.

In screening for distant metastases second primary tumours can occasionally be detected at the same time, a potential secondary gain in this group of patients. Second primary tumours also have impact on survival and may alter the selection of therapy in HNSCC patients. The cumulative risk for second primary tumours in HNSCC patients is 3% per year. Synchronous second primary tumours are diagnosed in about 4% of the HNSCC patients. Although the head and neck region is the most frequent site, synchronous primary tumours also occur below the clavicles: lungs, oesophagus and other sites (7). Therefore, the detection of second primary tumours during initial work-up is important.

In a multicentre prospective study we found that whole body positron emission tomography (PET) using the radio-labelled glucose analog 2-deoxy-2-[¹⁸F]fluoro-D-glucose (FDG) has additional value in screening for distant metastases and second primary tumours, if applied to the subset of patients at substantial risk (8). An assessment of imaging examinations is usually based on a determination of their accuracy rates and sensitivity and specificity values. However, the clinical utility of an imaging study also depends on the reliability or the consistency with which the study is interpreted in the same way by different observers. The consistency of observations made by different observers in interpreting the same studies is termed interobserver reliability or agreement. Although the accuracy rates of CT and PET for screening on distant metastases in HNSCC patients

have been determined and compared in several studies, the interobserver reliabilities of these diagnostic techniques have not been measured. The extent to which these accuracy results found by individual observers can be generalized, and thereby foresee the applicability of CT and PET for this patient group in daily clinical practice, tends to depend on the degree of uniform reporting by different observers. This study was performed to evaluate the interobserver variability in reporting of CT and PET for screening on distant metastases in HNSCC patients.

Materials and Methods

Chest CT and whole body ^{18}F FDG-PET of 69 HNSCC patients (18 women and 51 men) with high-risk factors who underwent screening for distant metastases in our institute were analyzed. The protocol was approved by the institutional ethics committee. Since these examinations are performed in routine clinical practice no informed consent was asked.

The mean age was 59 years and ranged from 40 to 81 years. Primary tumour sites included the oral cavity (n=12), oropharynx (n=25), hypopharynx (n=16), larynx (n=10), cervical oesophagus (n=4) and lymph node metastases of unknown primary tumour (n=12). Eight patients had two or more synchronous primary tumours. Indications (based on palpation, CT, MRI, and/or ultrasound-guided fine-needle aspiration cytology) for screening for distant metastases were three or more lymph nodes metastases (n=8), bilateral lymph metastases (n=19), lymph node metastases of 6 cm or larger (n=16), low jugular lymph node metastases (n=2), regional tumour recurrence (n=8) and second primary tumours (n=21). Some patients had more than one indication for screening. All were candidates for extensive treatment with curative intent: surgery and/or radiotherapy with or without chemotherapy.

In 67 of the 69 patients a chest CT, which was performed to screen for lung metastases, mediastinal lymph node metastases and second primary bronchogenic carcinoma, was available for review. Spiral CT scans were obtained with a fourth-generation Siemens Somatom Plus (Siemens AG, Erlangen, Germany after intravenous administration of contrast medium (Ultravist, Schering AG, Berlin, Germany). Contiguous axial scanning planes were used with a 5-mm slice thickness without interslice gap. All images were reviewed on PACS. Size was measured with manual electronic measurement. The volume of intravenous contrast was 100 ml at 3 ml per second with a delay of 25 to 30 s. Radiological criteria for lung metastases were: smoothly defined and subpleurally located lesions, multiple and located at the end of a blood vessel; for bronchogenic carcinoma, solitary, spiculated, and centrally located lesions; and for mediastinal lymph node metastases, a short axial diameter of more than 10 mm (9).

All 67 chest CT scans were independently read by two experienced radiologists (RPG, JHW) who were blinded to the other examinations and follow-up results. On special forms

location, long-axis diameter (<1, 1-2, 2-3, >3 cm), origin (metastasis, second primary, benign) and a five point ordinal Likert-scale score (1=definitively benign, 2=probably benign, 3=equivocal, 4=probably malignant, 5=definitely malignant) of the most suspected lesions (with a maximum of 5) were scored. Finally a conclusion had to be made for the presence (yes, no or equivocal) of metastases or second primary tumour. Spiculations were included in the determination of the long-axis diameter. If a nodule was visible on several adjacent images, the largest diameter was selected.

All 69 patients underwent ^{18}F FDG-PET after a 6-h fast. At 90 minutes after the intravenous administration of 10 mCi (370 MBq) ^{18}F FDG imaging of the body (trajectory: knee-skull) was performed using a dedicated PET scanner (Siemens HR plus). Any focal abnormality suspicious for malignancy was reported. Although the primary goal was screening for distant metastases, second primary tumours were additionally scored as an event. As with CT, PET images of the 69 patients were scored by two independent experienced nuclear physicians (OSH, EFC). ^{18}F FDG uptake was considered abnormal in cases of enhanced uptake incompatible with its physiological biodistribution. The interpreters used special forms to register the location and aspect ('focal' or 'diffuse') of lesions in PET scans, and to assign a Likert score to grade their suspicion of malignancy (of the most suspected lesions). Finally, a conclusion had to be drawn for the presence (yes, no, equivocal) of metastases or second primary tumour. The 'aspect' of lesions was included since this is one of the elements that helps with interpretation: areas of diffusely enhanced uptake are more likely to be inflammatory than focal ones. Like CT, differentiation between primary and secondary lesions can be difficult with PET; in the present study the reviewers classified central pulmonary lesions in PET scans as suspicious of primary tumours, and peripheral lesions as metastases unless there were additional lesions in PET scans (e.g. mediastinal foci) suggesting the presence of a second primary tumour and its metastases. No standard uptake value was calculated. No axis of a lesion was measured, because PET does not reliably estimate tumour size.

The interobserver agreement was determined and expressed in a weighted or unweighted kappa which corrects for agreement by chance. The higher the kappa, the higher the agreement, with a maximum of 1.0: < 0 = no agreement, 0.0-0.19 = poor agreement, 0.20-0.39 = fair agreement, 0.40-0.59 = moderate agreement, 0.60-0.79 = substantial agreement, 0.80-1.00 = almost perfect agreement (10).

In case of disagreement between the two observers a final consensus reading was performed. Any change in scoring was reported.

To correct for difference in scanning separate analysis was performed for lesions inside the thorax. To examine the role of the spatial resolution separate analysis was performed for lesions < 1 and ≥ 1 cm (on CT scan).

Results

In 39 patients of the 67 patients no suspected lesions were found by chest CT. In the remaining 28 patients a total number of 109 lesions on CT were scored (62 by observer 1 and 47 by observer 2). In 43 of the 69 patients no suspected lesions were found by PET. In the remaining 26 patients a total number of 94 lesions on PET were scored (47 by observer 1 and 47 by observer 2). The scorings of the observers and the kappa values are shown in Table 1.

Table 1. Scorings of the observers with interobserver agreement as kappa-values

	CT		kappa	PET		kappa
	Observer 1	Observer 2		Observer 1	Observer 2	
PER LESION	N= 62	N= 47		N= 47	N= 47	
long-axis diameter			0.516	N/A	N/A	N/A
< 1cm	34	26				
1-2 cm	21	17				
2-3 cm	4	1				
> 3cm	3	3				
origin			0.406*			0.834*
metastasis	30	19		15	14	
second primary	9	12		11	11	
benign	23	16		21	22	
Likert			0.512			0.939
definitively benign	5	6		0	0	
probably benign	17	10		10	12	
equivocal	10	10		9	7	
probably malignant	13	12		21	21	
definitively malignant	17	9		7	7	
OVERALL CONCLUSION	N=67	N=67		N=69	N=69	
malignancy			0.634*			1.000*
yes	13	10		15	15	
no	54	57		54	54	
metastasis			0.523			0.820
yes	8	6		11	9	
equivocal	6	6		3	4	
no	53	55		55	56	
second primary tumor			0.517			0.826
yes	6	6		7	8	
equivocal	2	3		2	2	
no	59	58		60	59	

* = unweighted kappa

The kappa value for long-axis diameter on CT was 0.516 (95% confidence interval (CI) 0.357-0.675). For origin, Likert-scale score, malignancy, metastasis and second primary tumour the values were 0.406 (95% CI; 0.277 - 0.534), 0.512 (95% CI; 0.384 - 0.640), 0.634 (95% CI; 0.387 – 0.881), 0.523 (95% CI; 0.226 – 0.780) and 0.517 (95% CI; 0.236 – 0.798), respectively. The long-axis diameter cannot be measured on PET. The kappa values for origin, Likert-scale score, malignancy, metastasis and second primary tumour were 0.834 (95% CI; 0.699 - 0.969), 0.961 (95% CI; 0.909 – 1.000), 1.000 (95% CI; 1.000 – 1.000), 0.820 (95% CI; 0.648 – 0.992) and 0.826 (95% CI; 0.633 – 1.000), respectively.

Initial disagreement in overall conclusions between the examiners occurred in eight CT examinations. The examiners could reach consensus in all cases. After consensus reading observer 1 changed his diagnosis five times: three times from second primary to no malignant lesion and two times from no malignancy to metastasis. Observer 2 changed his diagnosis four times: two times from no malignancy to metastasis, one time from equivocal to metastasis and one time from metastasis to no malignancy.

Initial disagreement in overall conclusions between the examiners occurred in five PET examinations. Also for PET the examiners could reach consensus in all cases. After consensus reading observer 1 changed his diagnosis three times: two times from metastasis to second primary tumour and one time from metastasis to unclear. Observer 2 changed his diagnosis two times: both times from metastasis to second primary tumour.

Lesions outside CT scanning range

Seven lesions were observed outside of the thorax. Three lesions were localized in the rectum and 2 lesions in the colon. All of these lesions were according to both observers not suspicious for malignancy (focal polyps). One lesion was localized in the liver. This lesion was scored as probably malignant by both observers. One lesion was localized in the lumbar spine and was scored as being definitively malignant by both observers. If lesions outside of the thorax were left out, the kappa for PET interobserver agreement were as follows: origin 0.811 (95% CI; 0.637 – 0.985); Likert 0.971 (95% CI; 0.916 – 1.000); malignancy 1.000; metastases 0.740 (95% CI; 0.521 – 0.959) and second primary tumour 0.858 (95% CI; 0.698 – 1.000).

Nodules < 10 mm

In a total of 18 patients, lesions < 10 mm on CT were reported. In 11 out of 18 patients in whom lesions < 10 mm were reported on CT no lesions were seen on PET (both observers negative). For lesions < 10 mm (as measured by CT observer 1) the kappa values for CT interobserver agreement were: origin 0.308 (95% CI; 0.009 – 0.606); Likert 0.411 (95% CI; 0.150 – 0.671); malignancy 0.558 (95% CI; 0.411 – 0.705); metastases 0.444 (95% CI; 0.156 – 0.733) and second primary tumour 0.627 (95% CI; 0.383 – 0.870). For PET these figures were 1.000 for all variables. For the other lesions (≥ 10 mm) the kappa values for CT interobserver agreement were: origin 0.535 (95% CI; 0.227 – 0.843); Likert 0.469 (95%

CI; 0.178 – 0.760); malignancy 0.524 (95% CI; 0.387 – 0.661); metastases 0.509 (95% CI; 0.267 – 0.752) and second primary tumour 0.339 (95% CI; 0.102 – 0.576). For PET these figures were: origin 0.811 (95% CI; 0.659 – 0.963); Likert 0.955 (95% CI; 0.894 – 1.000); malignancy 1.000; metastases 0.801 (95% CI; 0.630 – 0.972) and second primary tumour 0.898 (95% CI; 0.784 – 1.000).

Discussion

To be consistently useful, interpretation of imaging techniques must be reproducible. Ideally, both physicians with or without special expertise in a particular area will provide consistent interpretations. Although some accuracy data of chest CT and PET in screening for distant metastases have been determined and compared the interobserver variability of CT and PET in have not been measured (1, 4-8, 11).

CT is extremely sensitive in the detection of pulmonary nodules but is frequently indeterminate in diagnosis. Increasing numbers of pulmonary nodules are being detected, in large part due to the recent developments in CT imaging techniques. While specific patterns of calcification or the presence of fat in pulmonary nodules on CT can be used to determine if a nodule is benign, most nodules lack benign characteristics and are therefore considered indeterminate for malignancy. These non-calcified nodules represent a diagnostic challenge (12). Interobserver agreement for the detection of individual pulmonary nodules on CT is reported to be relatively poor. Wormanns et al (13) reported that of a total of 286 nodules, 103 nodules were found accordingly by both readers. Leader et al (14) scored 293 low-dose chest CT scans as to their probability of being benign or malignant nodule-based and examination based interobserver agreement among the three radiologist was poor: highest kappa value in paired comparison 0.120 and 0.458, respectively. In the present study a substantial amount of agreement (kappa 0.634) was found for scoring the presence or absence of malignancy using CT, whereas the agreement for this scoring was optimal (kappa 1.000) using PET. Also a five point ordinal Likert-scale was used to classify the level of susceptibility for malignancy. The interobserver agreement for CT findings was moderate (kappa 0.512), whereas for PET a high agreement (kappa 0.939) was found using five point ordinal scoring. These findings emphasize the difficulty in interpretation of pulmonary nodules on CT. As with CT, reading a PET scan requires weighing several factors to arrive at a diagnostic probability. There is no mathematical formula to cover them all. After detection, the interpretation process of a lesion involves several observer-dependent components, and this was one of the reasons for studying the observer variation. As in the present study Joshi et al (15) found a very high interobserver agreement for the evaluation of pulmonary nodules by PET as assessed with interclass correlation coefficients of 0.93 (range from 0 to 1). On PET images lesions are more or less 'present' or 'absent' and therefore probably less susceptible for variation in interpretation. In the presented study this is reflected in the facts that PET detected fewer

lesions < 10 mm, but the lesions which were seen were scored with an optimal interobserver agreement (kappa 1.0).

On CT, differentiation between a solitary pulmonary metastases and a second primary bronchiogenic carcinoma may be difficult. Therefore, most studies report on intrathoracic malignancies without separating metastases from primary tumours. In the present study the origin of lesions were scored by both CT and PET observers. The agreement on origin for the CT observers was moderate (kappa 0.406) and for PET observers high (kappa 0.834). Also the agreement in overall conclusion if pulmonary metastases were present was higher with PET as compared to CT observers (kappa 0.820 versus 0.523, respectively). Also for the conclusion if a primary bronchiogenic carcinoma was present or not, a higher interobserver agreement was found for PET than CT (kappa 0.826 and 0.517, respectively).

In certain clinical settings accurate assessment of the size of pulmonary nodules is important. In screening for distant metastases not the size but the nature (benign or malignant) and type (metastases or primary tumour) of the lesions are important. Only for detection of growth of small equivocal pulmonary nodules at follow-up suggestive of malignancy exact size measurement is warranted. Reports describing interobserver agreement for sizing nodules have been mixed. Hopper et al (16) evaluating interobserver variability in the measurements of metastases to the lung and liver on CT demonstrated statistically significant interobserver variability of 15%. Bogot et al (17) found a statistically significant interobserver variability in measuring pulmonary nodule volumes. Revel et al (18) found that both intra- and interobserver agreement for measurement of nodule size (long-axis diameter) on CT scans was poor. This is especially true for irregular and poorly defined tumour foci (16). On the contrary, Wormanns et al (13) assessed the interobserver variability in size determination of pulmonary nodules at spiral CT. In 23 patients with known pulmonary nodules diagnostic confidence and size in exact size measurement and categorization into three size classes (≤ 5 , 6-10, > 10 mm) were scored by two observers. A good correlation (Pearson's correlation coefficient 0.89-0.95) of measurements in millimetres was found. A good interobserver agreement in categories (kappa 0.74) was reported (11). In the present study a moderate amount (kappa 0.516) of agreement was found in categorization of size classes using CT. This agreement may be slightly different in newer generation CT scanner. In automated volume measurements interobserver agreement is less relevant.

In the present study reading in consensus changed the diagnosis (metastasis or second primary tumour) in 6% for CT and 7% for PET. This implies that probably in a subset of scans reading by two observers may be helpful.

In the present study in all categories the interobserver agreement of PET was higher as compared to CT. PET detected 47 lesions in 26 patients, while CT detected 69 lesions in 28 patients. Tumour size is an important determinant of the ability of PET to detect smaller lung malignancies. While no absolute size criteria is established, it is generally accepted that lesions less than 10 mm are predisposed to false negative results on PET

due to limited spatial resolution or low overall tumour volume. The limited spatial resolution of PET together with nodule motion from respiration at image acquisition may also impact the accurate detection of small pulmonary nodules (19). If visualized by PET the nature of the lesion is probably less difficult to determine than CT which depicts much smaller lesions. Scoring CT is probably more difficult because more lesions are visualized. It is anticipated that the use of newer generation CT-scanners and software, e.g. Computer Aided Detection, yield in increase of detection of (small) lung lesions (20). These technical improvements may result in a higher sensitivity. However, as is shown in this study the detection of smaller lesions is accompanied by a lower interobserver agreement. Combined reading of CT and PET may be helpful in lesions with a size that can theoretically be visualized by PET. In those lesions PET can aid in adding certainty in scoring the level of malignancy.

Because the data were acquired before PET-CT was widely available and became the standard, in the present study stand-alone PET rather than PET-CT has been used. However, we think that the most findings are still of relevance. PET and CT were compared in a head-to-head comparison. Even though PET-CT is becoming more prevalent now, and some comparative issues encountered with stand-alone systems will become less problematic, we feel that the first step of interpretation of PET-CT images should be an independent review of PET and CT. Combined readings thereafter will allow a joint estimate of the probability of disease.

Conclusion

In screening for distant metastases in HNSCC patients with high-risk factors chest CT readings had a reasonable to substantial agreement for size, origin and susceptibility of lesions, while PET readings showed an almost perfect agreement for lesion characteristics. These findings suggest that for optimal assessment in clinical practice PET most often can be scored by one observer, but CT should probably more often be scored by different observers in consensus or combined with PET.

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Chapter 5

Screening for distant metastases in head and neck cancer patients using ^{18}F FDG-PET and chest CT: validation of an algorithm

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Abstract

In patients with head and neck squamous cell carcinoma and high risk factors, the combination of whole body ^{18}F FDG-PET and contrast enhanced chest CT has the highest sensitivity and accuracy when screening for distant metastases. The aim of the present study was to retrospectively validate an earlier developed algorithm for interpreting the combination of screening with ^{18}F FDG-PET and CT. The test cohort consisted of 47 consecutive HNSCC patients with high risk factors for distant metastases, who had previously undergone ^{18}F FDG-PET and CT and had a minimum 12 months of follow-up. In 12 (26%) patients, distant metastases were detected during screening or within 12 months follow-up. In patients with locoregional control during follow-up the sensitivity and specificity were 55% (95% CI: 23-83%) and 97% (95% CI:82-99%) respectively for chest CT, 55% (95% CI:23-83%) and 100% (95%CI:88-100%) respectively for ^{18}F FDG-PET and 73% (95%CI:39-94%) and 100% (95%CI:88-100%) respectively for the combination of ^{18}F FDG-PET and CT. The proposed algorithm was considered to have been validated. In this algorithm all ^{18}F FDG-PET positive scans for distant metastases (regardless of interpretation of a solid lung lesion on CT) and CT scans with suspicious pulmonary lesions of less than 5 mm diameter (regardless of ^{18}F FDG-PET findings) are considered positive for distant metastases.

Introduction

Head and neck squamous cell carcinoma (HNSCC) accounts for approximately 5% of all malignant tumors worldwide. Two thirds of the patients with HNSCC present with advanced stage disease. HNSCCs have a proclivity to metastasize to regional lymph nodes rather than to spread hematogenously. Distant metastases usually occur late in the course of the disease and their presence influences prognosis and choice of treatment. Over the last 2 decade the success of locoregional treatment has improved significantly, which has resulted in a larger number of patients at risk of developing second primary tumours and distant metastases (1).

Patients with HNSCC and distant metastases are generally not considered curable and often receive palliative treatment alone. Therefore, screening for distant metastases is important in order to avoid unnecessary or inappropriate treatment.

Screening for distant metastases in all HNSCC patients is not routinely performed because the reported prevalence of clinically identified distant metastases is generally considered too low. The highest prevalence is found in patients with advanced stage disease and extensive lymph node metastases (2). In previous studies (3) we have identified and validated (4) the following high-risk factors for the development of distant metastases: ≥ 3 lymph node metastases, bilateral lymph node metastases, lymph node metastases ≥ 6 cm diameter, low jugular lymph node metastases, tumour recurrence (especially regional) and second primary tumours.

Positron emission tomography (PET) using the radiolabeled glucose analogue ^{18}F -fluorodeoxyglucose (^{18}FDG) has shown its potential to detect distant metastases (5). In a prospective multicenter study (SCHOOL) the diagnostic value of contrast enhanced chest CT (CE-CT) and whole body ^{18}FDG -PET for the detection of distant metastases were investigated in 92 evaluable patients with the aforementioned high-risk factors (6). The combination of PET and CT appeared to have the highest sensitivity and accuracy in screening for distant metastases. In addition, the criteria for interpreting the combined PET and CT results were refined using ROC (receiver operated characteristics) curves and logistic regression analysis of the CT and PET results scored using a five point ordinal scale: if CT and PET are both positive, distant metastasis is very likely to be present; if CT is positive and PET is negative the final assessment of the combined reading depends on the size of the lesion on CT (for small lesions below the detection limit of PET, outcome is predicted by CT, while for larger lesions PET adds extra information and these lesions are considered negative); if CT is negative and PET is positive, the final assessment of the combined reading depends on the location. The algorithm for lesions based on this previous study is shown in Figure 1. Because of the current PET detection limit, a 5 mm diameter is used as the cut-off value (6). In order to validate this algorithm we conducted a retrospective cohort study of patients with HNSCC and high-risk factors for dissemination, who had previously undergone screening for distant metastases using whole body ^{18}FDG -PET and CE-CT of the chest.

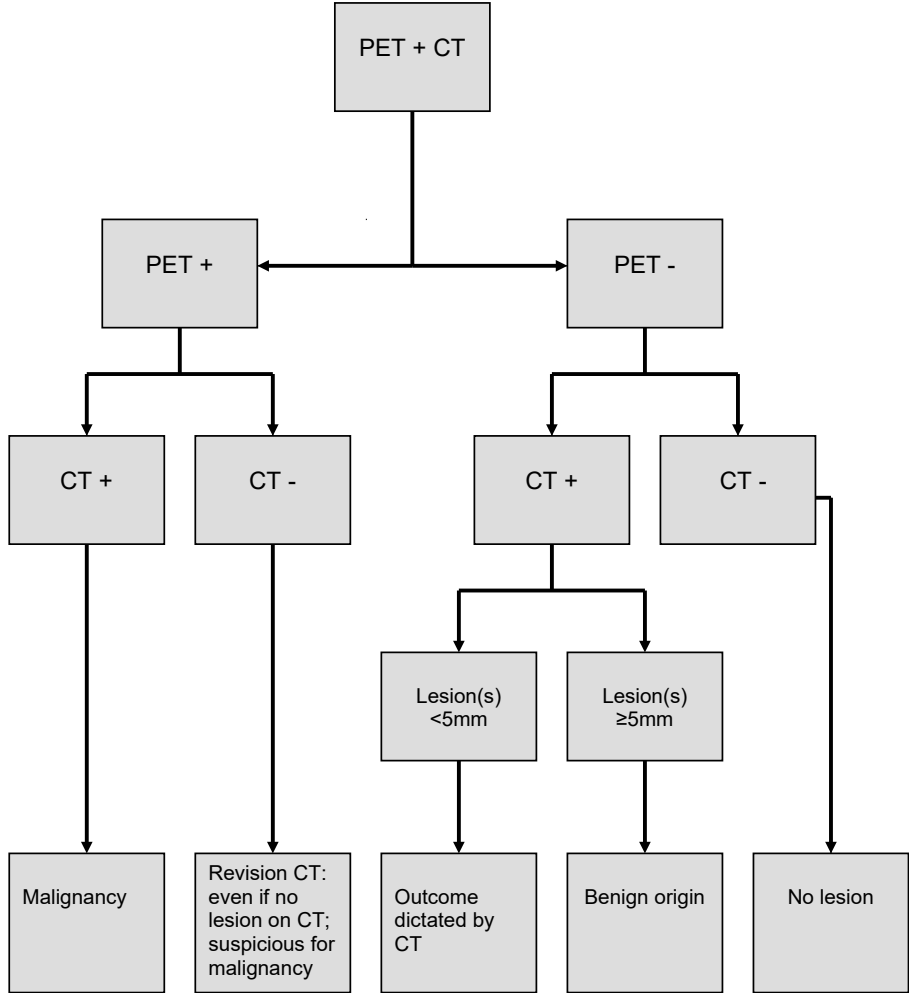


Figure 1. Inclusion of patients.

Materials and methods

A single-institution (VU University Medical Center, Amsterdam, The Netherlands) retrospective cohort study of screening for distant metastases tumours with CE-CT of the chest and whole body ^{18}F FDG-PET was performed. Patients who met the following criteria were eligible: 1. HNSCC; 2. candidates for radical treatment with curative intent (surgery and/or radiotherapy with or without chemotherapy); 3. a minimum of 12 months follow-up if no distant metastases or second primary tumour were detected at screening; 4. High-risk factors for the development of distant metastases. Forty-seven patients (35 men and 12 women) with a mean age of 61 years (range 45 – 86) were identified who

met these criteria. They had the following high-risk factors: ≥ 3 lymph node metastases (n=5), bilateral lymph node metastases (n=23), lymph node metastases ≥ 6 cm (n=2), low jugular lymph node metastases (n=6), (regional) tumour recurrence (n=5) and second primary tumours (n=16), as assessed by palpation, CT, MRI, and/or ultrasound-guided fine-needle aspiration cytology. Some patients had more than one high-risk factor. Primary tumour sites were the oral cavity (n=11), oropharynx (n=20), hypopharynx (n=7), larynx (n=6), cervical oesophagus (n=1) and regional recurrence (n=4). Two patients had synchronous second primary tumours.

Imaging techniques

All patients underwent CE-CT of the chest and whole body ^{18}F FDG-PET, in an order dictated by logistics. Spiral CT scans were obtained with a fourth-generation Siemens Somatom Plus (Siemens AG, Erlangen, Germany) after intravenous administration of contrast medium (Ultravist, Schering AG, Berlin, Germany). Contiguous axial scanning planes were used with a 5-mm slice thickness without an inter-slice gap. Radiological criteria for: (1) lung metastases, were: smoothly defined, sub-pleural suspicious lesions, multiple lesions and lesions located at the end of a blood vessel, and (2) bronchogenic carcinoma, were: solitary, spiculated, and centrally located lesions.

^{18}F FDG-PET was performed after a 6-hour fasting period with ample access to water. At 60-90 minutes after the intravenous administration of 250-370 MBq FDG, imaging with a trajectory from knee-skull base was performed using a dedicated full ring BGO PET scanner (CTI/Siemens ECAT HR+). Any focal abnormality, which could not be attributed to normal physiological uptake was considered suspicious for malignancy.

Data analysis

All ^{18}F FDG-PET scans and CT scans were retrospectively scored by one nuclear medicine physician and one radiologist respectively, with each blinded to the other modality and clinical outcome. For clinical decision making, these scan readings were scored as being either positive or negative for distant metastases. Combined reading of the CT and PET with side-by-side visual correlation was performed by a nuclear medicine physician and a radiologist using the proposed algorithm (Figure 1).

In all patients (with or without a synchronous second primary tumour) every lesion that was identified was also given a score to indicate how suspicious it was considered to be for a distant metastases. A five point ordinal Likert-scale was used: 1=definitely benign, 2=probably benign, 3=equivocal, 4=probably malignant, 5=definitely malignant. If multiple lesions were scored in a single patient, the lesion with the highest score was used for statistical analysis.

The outcome of the clinical diagnostic work-up and the clinical course between screening and when a follow-up period of 12 months had elapsed was used as the reference standard, and patients were classified as positive or negative with respect to the

presence of distant metastases. Follow-up was performed by regular visits to the outpatient clinic (every 6 weeks in the first year). During follow-up, the dates of the detection of distant metastases, second primary tumors and/or death were recorded. Although the primary goal was screening for distant metastases, second primary tumors were also registered. Initial screening was classified as true positive if there were evident metastases on chest CT, if lesions on chest CT were progressive or if biopsy (obtained by, for example, bronchoscopy, thoracoscopy, or thoracotomy) revealed metastasis. ^{18}F FDG-PET was considered true positive if a site of increased uptake was proven to be malignant by histopathology obtained by using one of the previously mentioned diagnostic techniques. If chest CT or ^{18}F FDG-PET had been abnormal during initial screening but further pre-operative work-up remained inconclusive, patients were treated as though they had no metastatic disease. If follow-up of 12 months did not reveal metastases, such suspicious CT or ^{18}F FDG-PET results were classified as false-positive. If a patient had a negative chest CT or ^{18}F FDG-PET, but developed distant metastases during the 12 month follow-up period, screening was considered to have been falsely negative. Screening by chest CT or ^{18}F FDG-PET was considered true negative if a patient had negative test results and no distant metastases were observed within 12 months.

Patients with negative screening results who manifested distant metastases within 12 months of follow-up were stratified for the presence or absence of locoregional control, because no distinction could be made between growth of subclinical metastases already present at the time of screening and reseeding from a locoregional recurrence. Although the primary aim of screening is to find distant metastases, detection of second primary tumours is an additional, clinically relevant finding. Patients with second primary tumours found during screening or follow-up were analyzed separately.

Statistical analysis

Sensitivity, specificity and accuracy of CT, PET and the combination of both were calculated with the corresponding exact 95 % confidence interval (CI). Receiver operated characteristic (ROC) analysis was used as an objective measure to evaluate the overall accuracy of CT and PET. The highest Likert score of a suspicious lesion on either CT or PET was used and the level of significance as well as the Q-point (highest sensitivity/specificity) was calculated

Results

Pretreatment screening identified distant metastases in 8/47 patients (17%) and second primary tumours in 3/47 (6%). All patients with distant metastases were treated with palliative intent. One of the three patients with a second primary tumour had disseminated lung cancer (lung and bone metastases) and was also treated palliatively. The other two

appeared to have a second primary with limited stage disease and were treated with curative intent for both the HNSCC and the second primary tumour. In 17 of the total group of 47 patients (36%) distant metastasis (n=12; 26%) or a second primary tumour (n=5; 11%) were detected either during screening or within 12 months follow-up after screening. Both patients who developed a second primary tumour during follow-up also had lung metastases. Since it was impossible to determine on imaging if these metastases originated from the index HNSCC (and were therefore missed by screening) or from the second primary tumour, these patients were not included in the accuracy analysis for the detection of distant metastases. Hence, the accuracy data for the detection of distant metastases was calculated using 45 patients.

Chest CT

The clinical report of the screening chest CT was positive in 10/47 (21%) patients. Nine patients had distant metastases (n=6) or a synchronous second primary tumour (n=3). One patient had false positive findings. Eight of the 37 (22%) patients with a negative CT-scan at screening developed distant metastases (n=6; 16%) or a second primary tumour (n=2; 5%) within the 12 month follow-up period. For the detection of distant metastases CT had (in n=45 patients – see comment above) a sensitivity of 50% and a specificity of 97% (Table 1).

Table 1. Accuracy of CT, PET and the combination of PET and CT in the detection of distant metastases

Method	Sensitivity	Specificity	PPV	NPV	Accuracy
n = 45 patients	Percentage with 95% confidence interval				
CT	50 (21 - 79)	97 (84 - 99)	86 (42 - 99)	84 (69 - 94)	84 (71 - 94)
PET	50 (21 - 79)	100 (89-100)	100 (54-100)	85 (69 - 94)	87 (73 - 95)
PET and CT	67 (35 - 90)	100 (89-100)	100 (63-100)	89 (75 - 97)	91 (79 - 98)

PPV, positive predictive value; NPV, negative predictive value

¹⁸FDG-PET

The clinical report of the screening ¹⁸FDG-PET was positive in 9/47 (19%) patients. All of them had confirmed distant metastases (n=6; 13%) or a synchronous second primary tumour (n=3; 6%). Eight of the 38 (21%) patients with a negative PET at screening developed distant metastases (n=6; 16%) or a second primary tumour (n=2; 5%) within the 12 month follow-up period, yielding a sensitivity for the detection of distant metastases of 50% and a specificity of 100% (n=45, Table 1).

CT and PET combined

In the total group of 47 patients, 12 (26%) patients had either a positive CT or positive ¹⁸FDG-PET. Malignancy was found in 11 (23%) of these patients; 8 (17%) distant metastases and 3 (6%) second primary tumors. CT and PET combined were scored using the aforementioned algorithm. As noted, lesions < 5mm cannot be reliably identified using PET as

single screening modality. In these cases the assessment was predominantly dictated by the CT characteristics.

In the total group of 47 patients, 9 (19%) patients had a positive FDG-PET. Of these 9 patients, 7 (15%) also had a positive CT confirming distant metastases (n=4; 9%) or a synchronous second primary tumour (n=3; 6%). In the remaining two patients with negative CT, the scans were reviewed. One patient was still considered not to have any lesions, but went on to develop rib metastases during follow-up at the same site where the screening ^{18}F DG-PET was positive. Another patient had a positive pulmonary lesion with ^{18}F FDG-PET but CT was scored as negative for metastases. Review of the CT confirmed a lesion of 6 mm, which was scored as being benign. During follow-up however distant metastases were subsequently confirmed at this site.

In the total group of 47 patients, 38 (81%) had a negative ^{18}F FDG-PET. Three of those patients (6%) had a positive CT and 35 (74%) patients a negative CT. Of the three patients with a positive CT and negative PET, one patient had a lung lesion of 15 mm, which did not appear to be malignant during follow-up and two patients had multiple lesions of 4 mm which were confirmed during follow-up.

Six of the 36 (13%) patients with negative ^{18}F FDG-PET and CT developed distant metastases (n=4; 11%) or a second primary tumour (n=2; 6%) within the 12 month follow-up period.

For the detection of distant metastases using the combination of PET and CT (n=45) the sensitivity was 67% and the specificity was 100% (Table 1).

Second primary tumours

In 3 of the 47 (6%) patients, a second primary tumour was found during initial screening while 2 of the 47 (4%) patients developed a second primary tumour during follow-up. In 3 of the 5 patients both ^{18}F FDG-PET and CT were true positive for a bronchogenic carcinoma. In the other 2 patients, both ^{18}F FDG-PET and CT were negative during screening.

Scenario analysis

When only the 40 patients with locoregional control during follow-up were analyzed, the sensitivity to detect distant metastases increased from 50% to 55% with ^{18}F FDG-PET, from 30% to 55% with CT and from 67% to 73% with ^{18}F FDG-PET and CT combined using side-by-side visual correlation (Table 2).

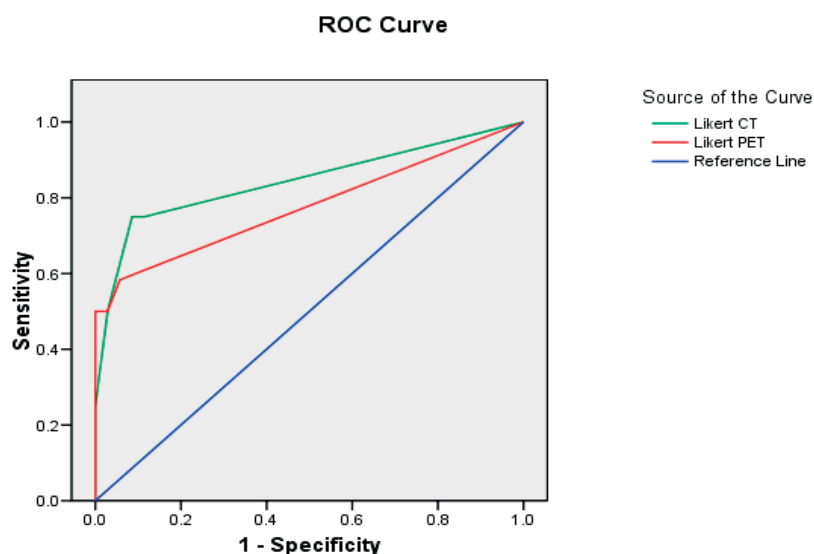
Table 2. Accuracy of CT, PET and the combination of PET and CT in the detection of distant metastases in patients with locoregional control

Method	Sensitivity	Specificity	PPV	NPV	Accuracy
n = 40 patients	Percentage with 95% confidence interval				
CT	55 (23 - 83)	97 (82 - 99)	86 (42 - 99)	85 (68 - 95)	85 (70 - 94)
PET	55 (23 - 83)	100 (88-100)	100 (54-100)	85 (69 - 95)	88 (73 - 96)
PET and CT	73 (39 - 94)	100 (88-100)	100 (63-100)	91 (75 - 98)	93 (80 - 98)

PPV, positive predictive value; NPV, negative predictive value

Refined interpretation criteria

After all scans were scored according to the five point ordinal scale for the presence or absence of distant metastases ROC curves were constructed (Figure 2). If in one patient multiple lesions were scored, the lesion with the highest score was used for statistical analysis. Three patients in which a second primary tumour but no distant metastases were detected, scored negative (Likert = 0) with respect to the screening for distant metastases. ROC analyses provided areas under the curve (AUCs) of 0.84 and 0.78 for CT and PET, respectively (both significantly different from the null hypothesis [true AUC = 0.5]). The comparison of both AUCs showed no significant difference ($p=0.45$). The Q-point for PET was found at a five point ordinal scale score =1 for a sensitivity of 58% and a specificity of 94%. For CT this point lies at a score =3 with a sensitivity of 75% and specificity of 91%.



	Area under the curve	95% CI
PET	0.78	0.59 – 0.96
CT	0.84	0.69 - 1

Figure 2

Discussion

¹⁸FDG-PET and chest CE-CT have good diagnostic performance in detecting distant metastases in patients with HNSCC (7). However, scoring criteria and interpretation are not

well defined, resulting in different study outcomes. In the present study we validated an algorithm which was based on findings from our previous multicenter study on screening for distant metastases in HNSCC (6).

Using this algorithm on a test set of 47 patients with high-risk factors for dissemination, similar accuracy data for the detection of distant metastases by the combination of ^{18}F FDG-PET and CT were obtained as in the original study. In the group of HNSCC patients with locoregional control a sensitivity of 73% (95% CI: 39-94%), a specificity of 100% (95% CI: 88-100%), a positive predictive value of 100% and a negative predictive value of 91% were found. In the previous study using the same algorithm these figures were 82% (95% CI: 65-92%), 95% (95% CI: 88-98%), 86% (95% CI: 69-94%) and 93% (95% CI: 85-95%), respectively (6).

Regarding clinical relevance, the results of the Q-point and AUCs could suggest that Likert scoring does not add further information to the ^{18}F FDG PET and that when a lesion is seen on PET, it can mostly be regarded as being malignant. For CT the highest sensitivity is reached when the Likert score is 3 or higher. In our previous studies the cut-off point was found at Likert 4 or higher (6). Likert 3 lesions are typically small nodules, which are often the subject of debate regarding benign or malignant origin. The use of Likert scoring can probably not adequately resolve this matter. A substantial interobserver variability in CT interpretation was previously reported (8).

The pre-test probability of the patients and the prevalence of malignant disease influence the optimal scoring criteria and algorithm. The prevalence of malignancy in solitary pulmonary nodules (SPNs) ranges from 5 to 70% (9). Since the presence of distant metastases at pretreatment evaluation influences the prognosis and thus treatment selection, detection of distant metastases will alter the treatment plan and may avoid unnecessary or inappropriate treatments which present a burden and risks to the patient, affect quality of life, consume resources and result in costs (e.g. hospital stay, operating time and radiotherapy facilities) (10). False positive findings on imaging should have limited clinical consequence since confirmation by histopathology or further imaging is warranted before treatment with curative intent is withheld from a patient. Therefore, in screening for distant metastases sensitivity is to a certain extent more important than specificity.

The extent to which results found by different studies can be generalized, and support the application of CT and PET to this patient group in daily clinical practice, tends to depend on the degree of uniform interpretation using well defined scoring criteria. CT is extremely sensitive for the detection of pulmonary nodules but is frequently indeterminate in diagnosis. Increasing numbers of pulmonary nodules are being detected, in large part due to the developments in CT imaging techniques. While specific patterns of calcification or the presence of fat in pulmonary nodules on CT can be used to determine if a nodule is benign, most nodules lack benign characteristics and are therefore considered indeterminate for malignancy. Indeed, in a previous study a substantial amount of agreement was found for scoring the presence or absence of malignancy using CT, whereas the

agreement was almost perfect using PET (8). This emphasizes the difficulty in interpreting pulmonary nodules on CT. On PET images lesions are essentially 'present' or 'absent' which probably makes them less susceptible to variation in interpretation. We have suggested that for optimal assessment in clinical practice one observer is usually sufficient for scoring PET, but CT should probably more often be scored by more than one observer in consensus or combined with PET (8).

If multiple suspicious lesions are detected, malignancy is very likely. Solitary lesions are more difficult to assess. Orlicchio et al (11) defined indeterminate solitary pulmonary nodules (SPN) as single solid round or oval shape lesions smaller than 3 cm with no unequivocal signs of benign or malignant disease, normally ventilated peripheral parenchyma, absence of hilar or mediastinal nodal enlargement and no extrathoracic findings suggestive of distant metastasis. The assessment of SPN has been studied in different settings: incidental discovery and during the evaluation of cancer patients. Definite criteria for the differentiation of indeterminate SPNs by CT and ^{18}F FDG-PET have not been standardized and are still a matter of debate. Criteria to score an SPN as malignant on CT include location, size, volume doubling time and contrast-enhanced increase in attenuation (11,15).

Scoring criteria for ^{18}F FDG-PET interpretation of an SPN as malignant include hypermetabolic activity greater than the mediastinal blood pool and a (semi)quantitative standardized uptake value (SUV) higher than a certain threshold value (16,17). Since different methods to assess the ^{18}F FDG-avidity are used, studies may be difficult to compare (18). Several studies have found no significant difference between the diagnostic performance of visual interpretation and (semi)quantitative analysis of ^{18}F FDG-uptake (16,17). Pulmonary lesions with visually absent ^{18}F FDG uptake indicate that the probability of malignancy is very low, while this probability in any visually evident lesion is about 60% (19). This supports our recommendation to consider each positive ^{18}F FDG-PET as malignant regardless of the CT interpretation of solid lesions.

Limitations in PET camera resolution hamper the evaluation of nodules less than 8 mm in diameter (19). In lesions less than 10 mm CT has added value to PET. De Wever et al (20) found a sensitivity of 100% for the combination of PET and CT compared to 83% for PET only in nodules less than 10 mm (the majority were 5-10 mm) in diameter (20). Fortes et al (21) found in patients who underwent lung resection for pulmonary metastases from extrathoracic malignancies a significant correlation between the size of the nodule and the sensitivity of ^{18}F FDG-PET: 30% of the metastatic nodules of 10 mm or smaller were ^{18}F FDG-PET positive, while in nodules larger than 10 mm this figure was about 88% (21). A meta-analysis of 1474 pulmonary nodules evaluated by ^{18}F FDG-PET revealed an overall high specificity, but varying sensitivity for nodules less than 1 cm (22). Other studies also found a higher rate of erroneous ^{18}F FDG-PET results for lesions < 10 mm compared to larger lesions (23-25). However, in indeterminate SPNs greater than or equal to 7 mm PET is more useful than CE-CT due to its high sensitivity and much better specificity (14). Divisi et al (26) compared the results of CT and PET/CT in patients with asymptomatic

SPN with a diameter between 0.5 and 0.99 cm and between 1.0 and 1.5 cm and found that PET/CT can improve the identification and characterization of potentially malignant pulmonary nodules with a diameter less than 1 cm. In our algorithm there is an important role for PET for lesions > 5mm.

¹⁸FDG-PET lacks precise anatomical resolution and may lead to overdiagnosis of some inflammatory conditions. By virtue of its high spatial resolution, CT may serve as a cross-sectional imaging tool complementary to FDG-PET in the evaluation of distant metastases in HNSCC patients and may help to characterize ¹⁸FDG abnormalities. In recent years, dual modality PET-CT has been used to fuse functional PET and morphological CT data in a single examination. Fused ¹⁸FDG-PET/CT is increasingly being applied in detecting distant metastases in patients with HNSCC because of its unique capability to image metabolically active lesions and provide more anatomical details than PET only images. Moreover, fusion of ¹⁸FDG-PET and CT may more accurately localize the lesions. The combination of PET and CT by PET-CT is an attractive option, potentially combining the best of both imaging abilities, and providing one combined diagnostic study for the patient.

In conclusion, when screening for distant metastases in HNSCC patients with risk factors for dissemination, using whole body ¹⁸FDG-PET and CE-CT of the chest good performance can be obtained using the proposed algorithm in which all ¹⁸FDG-PET positive scans for distant metastases (regardless of the interpretation of a solid lung lesion on CT) and CT scans with suspicious pulmonary lesions of <5 mm (regardless of ¹⁸FDG-PET findings) are considered positive for distant metastases.

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Chapter 6

Pretreatment screening on distant metastases and head and neck cancer patients: Validation of risk factors and influence on survival

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Abstract

Previously identified high risk factors for development of distant metastases are: three or more lymph node metastases, bilateral lymph node metastases, lymph node metastases ≥ 6 cm, low jugular lymph node metastases, locoregional tumour recurrence and second primary tumours. The aims of this study were to validate these specific risk factors and to investigate the impact of time (i.e. during screening or follow-up) of detection of distant metastases on survival. From a total of 301 HNSCC patients with high risk factors who were scheduled for extensive treatment and underwent pretreatment screening on distant metastases using chest CT and/or whole body ^{18}F FDG-PET(/CT) (in some patients combined with whole body MRI), the high risk factors, the development and time point of distant metastases and survival were analyzed. Forty-four percent developed distant metastases. Multivariate analysis revealed that bilateral lymph node metastases were the strongest predictive factor. Locoregional recurrence and second primary tumours were the risk factors associated with the lowest cumulative incidence. However, if the risk factor locoregional recurrence was split into local and regional recurrences, regional recurrence was associated with a substantially higher risk than local recurrence. The more high risk factors a patient had the lower the 5-year distant metastases free survival was. Patients with distant metastases detected pretreatment had a significant worse survival (corrected for lead time bias) compared to patients with distant metastases diagnosed during follow-up. The validity of three or more lymph node metastases, bilateral lymph node metastases, low jugular lymph node metastases and regional recurrence as high risk factors for the development of distant metastases was confirmed. If more high risk factors are present the cumulative incidence of distant metastases increases significantly. The detection of distant metastases by pretreatment screening worsens the overall survival as compared to distant metastases detected during follow-up.

Introduction

In patients with head and neck squamous cell carcinoma (HNSCC) distant metastases usually occur late during the course of the disease (1,2). If distant metastases are present in general no curative options are currently available. Once distant metastases are detected, the prognosis is dismal. The median time to death from the diagnosis of distant metastases ranges from 1 to 12 months (1-7). About 88% of the patients with distant metastases will die within 12 months (1). Thus, the detection of distant metastases is critical for prognostication and for the choice of treatment in patients with HNSCC (3). Detection of distant metastases may avoid futile extensive locoregional treatments with unnecessarily burden to the patient affecting quality of life and use and costs of resources, e.g. hospital stay, operating time and radiotherapy facilities. These considerations affect therapeutic decision making at initial diagnosis as well as in the management of locoregionally recurrent disease.

The reported prevalence of clinically identified distant metastases in HNSCC at presentation varies from 2 to 18% (4,8,9), but this is generally considered too low to warrant routine screening for distant metastases in all HNSCC patients. Besides better diagnostic techniques, selection of patients with high risk factors may increase the yield of examinations for the detection of distant metastases.

Jäckel and Rausch (9) found that screening is particularly useful in patients with advanced stage disease, local and/or regional recurrences and second primary tumours. Loh et al (10) evaluated screening in HNSCC patients using chest CT and found T4 and/or N2 or N3 oropharyngeal, hypopharyngeal and supraglottic squamous cell carcinoma to be risk factors for the development of distant metastases: 64% of the patients with T4 and 73% of the patients with N2 or N3 disease had distant metastases detected during screening. These figures were significantly higher as compared to patients with tumors at other sites and lower T- or N-classifications (10). Leong et al (11) found in their series of 102 patients who underwent screening by chest X-ray and CT that of the patients with positive screening, 86% had T3 or T4 disease and 71% had N2 or N3 disease.

In a retrospective study in 101 patients with advanced HNSCC we identified risk factors for development of distant metastases: three or more lymph node metastases, bilateral lymph node metastases, lymph nodes larger than 6 cm, low jugular lymph node metastases, locoregional tumor recurrence and second primary tumours (4). Using these refined risk factors comparable high incidences of distant metastases were found in subsequent studies on the screening for distant metastases (12,13). Using these selection criteria, distant metastases were detected in 29-33% of the patients during initial screening (18-19%) or within 12 months follow-up after initial screening (11-14%). These studies validated the use of this set of risk factors to select patients at high risk for development of distant metastases.

The overall survival of HNSCC patients with distant metastases detected by pretreatment screening is significantly lower than patients with negative screening (12,14).

Brouwer et al [12] found a significantly better overall survival in patients who developed distant metastases during follow up compared to those with metastases at the time of pretreatment screening. Of the patients with distant metastases detected during follow-up, 60% survived longer than 12 months after initial treatment (12). However, Haerle et al (14) could not confirm this difference in overall survival. A survey in The Netherlands revealed that the majority of head and neck surgeons would refrain from extensive treatment if a HNSCC patient would develop clinically manifest distant metastases within 12 months (15). Screening for distant metastases may be helpful to select patients who are good candidates for extensive treatment.

The aims of this study were to validate these specific risk factors and to confirm the impact of time (i.e. during screening or follow-up) of detection of distant metastases on survival.

Material and methods

Patients who underwent pretreatment screening on distant metastases from 1997 till 2011 were retrospectively included in this study. Inclusion criteria were: (1) HNSCC, (2) candidates for extensive treatment with curative intent (surgery and/or radiotherapy with or without chemotherapy), (3) at increased risk for distant metastases (i.e.: ≥ 3 lymph node metastases (n=43), bilateral lymph node metastases (n=97), lymph node metastases of ≥ 6 cm (n=37), low jugular lymph node metastases (n=33), locoregional tumour recurrence (n=83) and second primary tumours (n=89)), as assessed by palpation, CT, MRI, and/or ultrasound-guided fine-needle aspiration cytology. Most patients were also included in previous studies on the accuracy of chest CT (n=109) ^{18}F FDG-PET (n=73) [12,13]. The other patients underwent screening as a routine procedure using ^{18}F FDG-PET and CT (n=47), ^{18}F FDG-PET-CT (n=52) or whole body MRI (n=20). The high risk factors, the development and time point of distant metastases and survival from a total 301 HNSCC patients were analyzed.

Of these patients 234 were male, the mean age was 61 years (range 33 - 86). Primary tumour sites were the oral cavity (n=78), oropharynx (n=118), hypopharynx (n=33), larynx (n=70), cervical esophagus (n=6), lymph node metastases of an unknown primary tumour (n=16), nasopharyngeal (n=3), neopharyngeal (n=1). Twenty-four patients had more than one synchronous primary tumour in the head and neck area. Six patients had a synchronous (primary) lung or hepatocellular tumour. These patients were not excluded because they did not develop distant metastases during screening or follow-up. In case of negative pretreatment screening on distant metastases, patients were treated with curative intent (despite high risk factors) and patients with positive screening by palliative treatment. Patients with high risk factors and negative screening were not treated differently from other patients not diagnosed with distant metastases.

Imaging techniques

Spiral CT scans were obtained with a third-generation Siemens Sensation 64 (Siemens AG, Erlangen, Germany) after intravenous biphasic administration of contrast medium (Ultravist, Schering AG, Berlin, Germany). Contiguous axial scanning planes were used with a 5-mm slice thickness. Radiological criteria for lung metastases were: smoothly defined and subpleurally located lesions, multiple and located at the end of a blood vessel; for bronchogenic carcinoma, solitary, spiculated, and centrally located lesions; and for mediastinal lymph node metastases, a short axial diameter of more than 10 mm.

¹⁸FDG-PET was performed after patients had fasted for 6 hours with ample access to water. At 60-90 minutes after the intravenous administration of 250-370 MBq ¹⁸FDG, imaging of trajectory knee-skull base was performed using a dedicated full ring BGO PET scanners (CTI/Siemens ECAT HR+). From 2007, patients were also scanned with a Gemini 64TF (Philips) PET-CT scanner. Any focal abnormality, suspicious for malignancy was reported.

See for more details on scoring criteria our previous studies (12,13).

Data analysis

The results of the clinical diagnostic work-up at presentation and follow-up were analyzed. Follow-up was performed by regular (each 4-6 weeks in the first year) visits to the outpatient clinic. The median follow-up for patients alive at the end of follow-up was 38 months (range 0-167). Detection of distant metastasis in follow-up was confirmed by imaging, in case of clinical suspicion in the outpatient clinic. During follow-up the dates of the detection of distant metastases, and death were recorded. Overall survival was defined as the time of screening (during pretreatment initial diagnostic work-up) until death. In this way survival was corrected for lead time bias of the detection of distant metastases by adding the time of initial diagnostic work-up to the survival after detection of distant metastases. Distant free survival was defined as time of screening until distant metastases were diagnosed. Time interval between diagnosis of distant metastases and death were calculated. CT- and ¹⁸FDG-PET-scans were evaluated by different attending staff radiologists and nuclear medicine physicians, respectively, according to common clinical practice.

Statistical analysis

For each separate risk factor the cumulative incidence of distant metastases at 5 year was calculated. Estimates of survival functions (distant free and overall survival) were computed by the Kaplan-Meier method for each risk factor and per number of risk factors (a patient had) and compared via the log-rank test. A p-value of <0.05 was considered statistically significant. For multivariate analysis a Cox regression analysis was used, with the method "Forced entry". These models enable the quantification of the influence of the predictive variables with regard to the development and time to detection (at diagnostic

work-up or follow-up) of distant metastases on survival. All calculations were carried out using SPSS 17.0 for windows.

Results

From the 301 eligible patients, 131 (44%) developed distant metastases. The cumulative incidence of distant metastases at 5 year for each risk factor is presented in Table 1. Multivariate analysis revealed that bilateral lymph node metastases is the strongest predictive factor. Locoregional recurrence and second primary tumor were the risk factors associated with the lowest cumulative incidence of distant metastases at 5 year. To analyze the weaker risk factor locoregional recurrence as risk factor more in detail we split this group in local recurrence and regional recurrence. The 5-year distant free survival rates are also shown in Table 1.

Table 1. The prognostic value of the high risk factors for distant metastasis, recurrence is split into local and regional recurrence of the tumor. Five-year distant metastasis free survival is analyzed using Kaplan Meier survival tables and univariate analysis with logrank analysis. Multivariate analysis of high risk factor predicting the occurrence of distant metastasis, using a cox regression analysis.

Variable	Cumulative incidence of distant metastasis (at 5 years)	5 year distant metastasis free survival	Univariate P value	Hazard ratio (multivariate analysis)	Multivariate P value
Three lymph nodes	63%	32%	0.029	1.46 (0.91-2.34)	0.120
Bilateral lymph nodes	59%	33%	0.006	1.56 (1.01-2.41)	0.043
Lymph node metastasis > 6cm	51%	27%	0.165	1.54 (0.88-2.70)	0.130
Low jugular lymph nodes	61%	34%	0.046	1.44 (0.88-2.37)	0.147
Locoregional recurrence	39%	55%	0.828	1.40 (0.81-2.42)	0.227
Local*	28%	69%	0.157**	0.99 (0.49-2.02)	0.983
Regional	50%	39%	0.159	1.81 (1.00-3.29)	0.052
Secondary primary	39%	59%	0.040	1.02 (0.59-1.75)	0.951

* The data dividing local and regional recurrence in multivariate analysis was obtained using a separate analysis entering local and regional recurrence as a categorical variable. The hazard ratio's are for local or regional recurrence compared to no locoregional recurrence. Only the resulting hazard ratio and p-value of local and regional recurrence are shown.

** Represents the p-value linked to difference in the occurrence of distant metastasis. Controversially patients with local recurrence had less distant metastasis in follow up compared to patients with no recurrence

For all risk factors distant free survival curves were constructed which are shown in Figure 1. Second primary tumour and local recurrent tumour seems to have the lowest risk of development of distant metastases. Distant metastases free survival curves according to the number of high risk factors a patient has are shown in Figure 2. The 5-year distant free survival was 54% for patients with exactly one risk factor, 33% for patients

with two risk factors, 17% in case of three risk factors and 0% for four risk factors (p=0.001, using the Log Rank test)

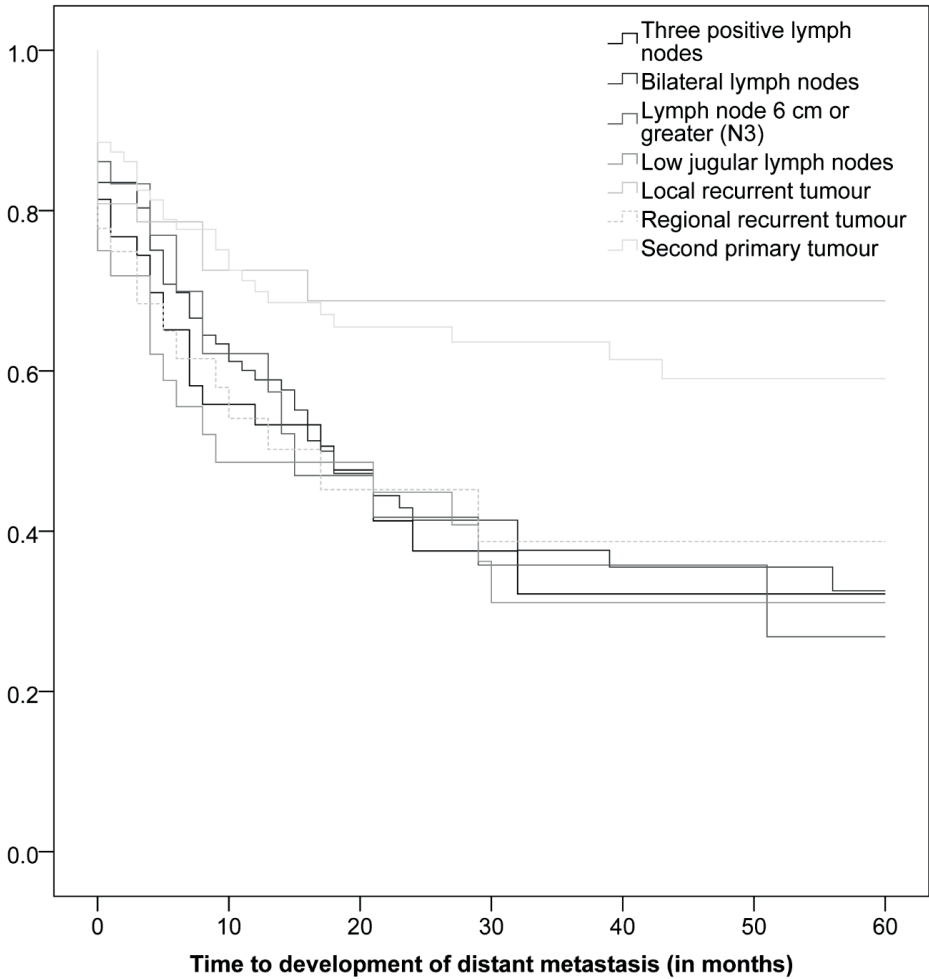


Figure 1. Kaplan-Meier curve of the time to development of distant metastasis (in months) for all risk factors

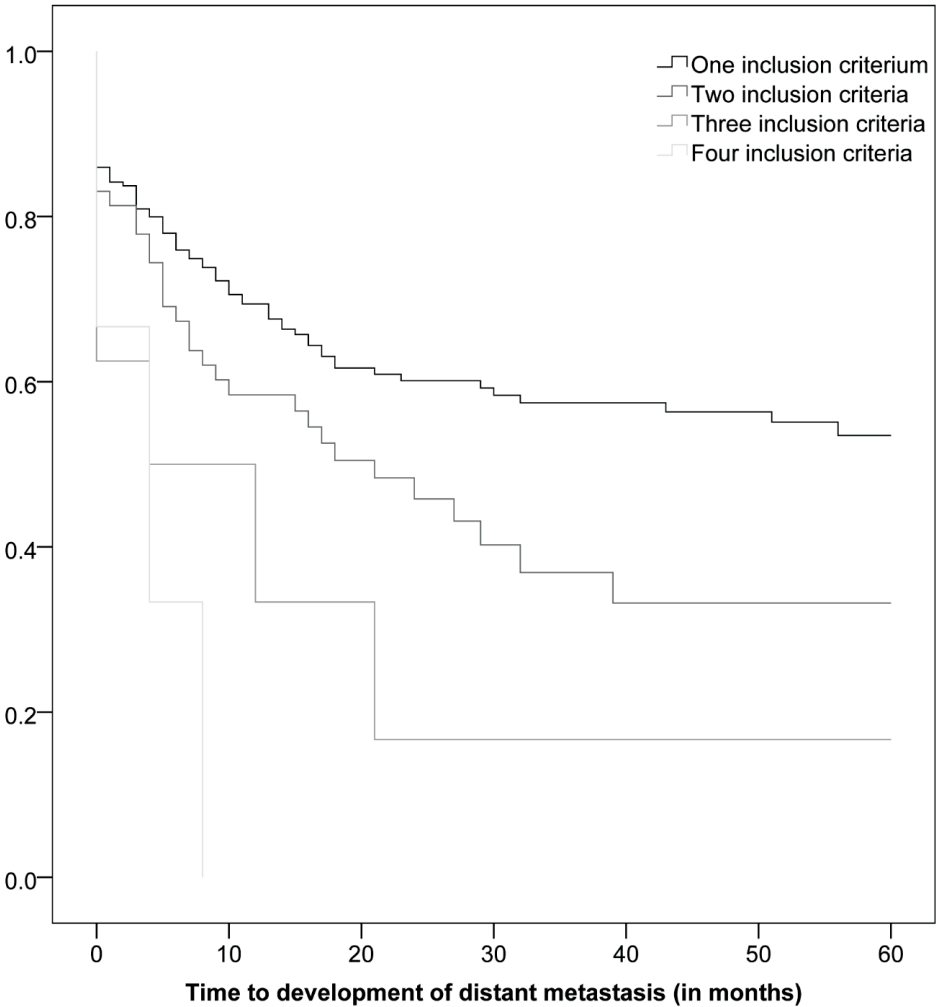


Figure 2. Kaplan-Meier curve of the time to development of distant metastasis (in months) according to the number of high risk factors. A significantly higher chance of developing distant metastasis is seen with a higher number of risk factors ($p = 0.001$).

The overall survival curves for patients without distant metastases, with distant metastases detected during screening and with distant metastases detected during follow-up are shown in Figure 3. The median time between screening and diagnosis of distant metastases during follow-up was 9 months (range 1-60), which was included (correction for lead time bias) in the overall survival time of patients in whom distant metastases were detected during follow-up. The 5-year overall survival for these groups of patients were 47%, 13% and 0%, respectively. There was a significant ($p < 0.001$) difference in overall survival with regard to the time of diagnosis of distant metastases (during screening or

follow-up): the median survival was 5 months (range 0-33) for patients with distant metastases detected by screening and 16 months (range 3-60) for patients with distant metastases detected during follow-up. The median interval between detection of distant metastases and death were (not corrected for lead time bias) 5 (range 0-33) and 2 (range 0-42), respectively.

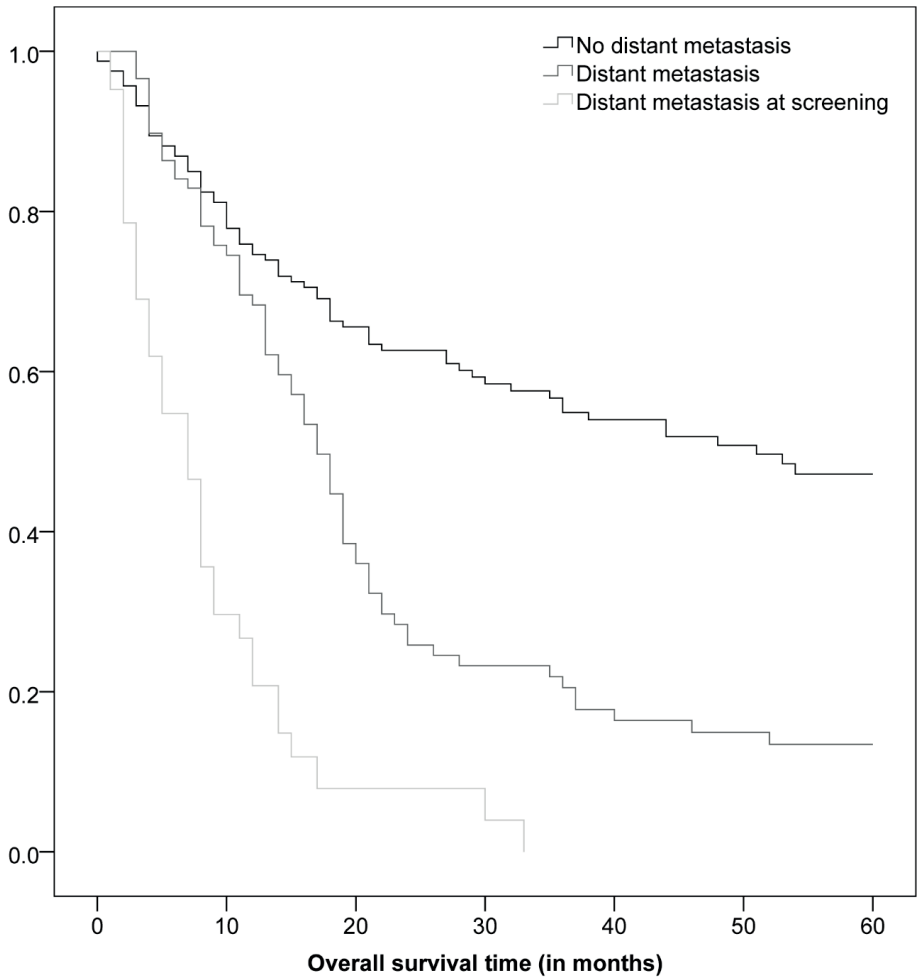


Figure 3. Five year overall survival of patients with recorded distant metastasis at the screening, distant metastasis in the follow-up after the screening, and patients with no recorded distant metastasis. Log-rank testing revealed a significant difference ($p < 0.001$) between the different patient groups

Discussion

In the present study the high risk factors were associated with the 5-year cumulative incidence of distant metastases ranging from 28 to 63%. These high cumulative incidences at 5 year justify the use of each of these risk factors for the selection of HNSCC patients who may benefit from screening on distant metastases without unnecessarily burden and use of resources. The risk factors three or more lymph node metastases, bilateral lymph node metastases, lymph nodes larger than 6 cm and low jugular lymph node metastases had the highest cumulative incidences of distant metastases. Bilateral lymph node metastases was the strongest predictive factor. Locoregional recurrence and second primary tumour were the risk factors associated with the lowest cumulative incidence of distant metastases within 5 year. However, if the risk factor locoregional recurrence was split into local and regional recurrence it appeared that regional recurrence is indeed a high risk factor whereas local recurrence itself is not. The more high risk factors a patient has the lower the 5-year distant metastases free survival was.

Kuperman et al (16) reported distant metastases in 2066 out of 73,247 (2.82%) HNSCC patients at presentation using the Surveillance Epidemiology and End Results (SEER) database. This low number of distant metastases in unselected HNSCC patients emphasizes the need for selection based on risk factors. Haerle et al (14) detected in 21% of patients with advanced stage disease (T3/4 and/or N2/3) distant metastases using ¹⁸FDG-PET-CT during screening and follow-up. In the present study refined risk factors were used resulting in the higher cumulative incidence of 45% after 5 year.

Several factors thought to bear an increased risk for distant metastases have been reported in the literature: tumors arising in the (supraglottic) larynx and pharynx, advanced clinically or pathologically determined T stage (T3 and T4), advanced N-stage (N2 and N3), stage IV and involvement of lower neck nodes (level IV/Vb), pathologically determined number of lymph node metastases, extranodal spread, poor differentiation grade of the primary tumour and tumour depth of invasion and locoregional recurrence, age and race (17-23). Unfortunately, in the pretreatment selection of patients who may benefit most from screening on distant metastases, risk factors obtained from the histopathological examination of the surgical specimen cannot be used. Moreover, some risk factors may not be independent risk factors.

Liao et al (23) found a higher 5-year distant metastases rate in patients with locoregional recurrence compared to patients with locoregional control (21.4% vs. 6.6%) (23). In the present study local recurrence is not a strong predictor, whereas regional recurrence appeared to be a strong predictor for distant metastases.

In screening for distant metastases also other (pretreatment) risk factors have been used. Ljumanovic et al (24) identified prognostic groups with MR imaging for the development of distant metastases. The low-risk group consisted of patients without MRI-positive nodes, the intermediate-risk group consisted of patients with MRI-positive nodes without signs of extranodal spread and the high-risk group consisted of patients with MRI-

positive nodes with signs of extranodal spread. Since extranodal spread on MRI is probably associated with advanced nodal disease, it may of interest to find out if radiological extranodal spread is a (better) prognostic independent of the high risk factors validated in the present study (24). Level of lymph node metastases, e.g. low jugular, posterior triangle and paratracheal metastases (depending on site of primary tumour) and contralateral lymph node volume were also predictors for the development of distant metastases [24]. These predictive factors are roughly incorporated in the validated risk factors of the present study. In a cohort of 299 patients with advanced stage HNSCC, Haerle et al (14) identified laryngeal and hypopharyngeal primary tumour sites and lymph node involvement of level IV/Vb as high-risk features in patients with advanced stage (T3/4 and/or N2/3) HNSCC. Level IV lymph nodes is one of the validated risk factors in the present study (24).

Several ¹⁸FDG-PET studies in HNSCC patients have found an association between standardized uptake values (SUV) of ¹⁸FDG in primary tumour and especially lymph node metastases and the development of HNSCC (22,25-28). Different cut-off values have been used to predict the development of distant metastases (Table 2). Since different methods to assess the ¹⁸FDG-avidity are used, studies may be difficult to compare (29).

Table 2. The predictive value of SUV max of the primary tumor and lymph node metastases in the several studies with different patient populations

	Primary / node	Cut-off value	Predictive	
Chan et al EJNM	Primary	12.5	-	All patients with oropharyngeal SCC
	Node	8.7	+	
Dibble et al	Primary		-	All (unselected?) patients with oral or oropharyngeal cancer
Haerle et al	Primary	9.0	-	Only patients with T3/4 and/or N2/3 HNSCC
Kubicek et al	Primary	8	-	All patients with head and neck cancer
	Node	10	+	
Liao et al IJROBP 2009	Node	5.7	+	Oral squamous cell carcinoma pN+ patients
Liao et al IJROBP 2010	Primary	8.6	+	Oral squamous cell carcinoma patients
	Node	5.7	+	
Yao et al IJROBP	Primary		-	All HNSCC patients who underwent IMRT
	Node	10.8	+	

Haerle et al (14) could not find an association between SUV max of the primary tumour and the development of distant metastases. Since only patients with T3/4 and/or N2/3 HNSCC were included, it can only be concluded that SUV max does not add to the risk of development of distant metastases for this advanced stage disease patients (14).

The diagnosis of distant metastases harbours a poor prognosis. The overall survival was significantly different if the distant metastases were diagnosed at the time of screening then if later during follow-up. This can be explained by a different biologic behavior

of the tumour but also different intention (non-curative) of treatment in patient with distant metastasis during pre-treatment screening. In the study of Haerle et al (14) the survival was not different for both groups if survival was corrected for delay in diagnosis (lead time bias) of distant metastases. Based on our previous (12) and present study, also corrected for lead time bias, it can be anticipated that screening on distant metastases can select patients with a short overall survival who will not benefit from extensive locoregional treatment. However, since pretreatment imaging has improved during the inclusion period (different imaging techniques have been used) and posttreatment screening on distant metastases was not routinely performed, these findings need confirmation by other studies.

In conclusion, the predictive value of most of the high risk factors for development of distant metastasis seems to be supported. Moreover the presence of multiple risk factors increases the cumulative risk of distant metastasis significantly. These risk factors can therefore be helpful in the selection of patients that have an increased risk of distant metastasis, and therefore the need for additional imaging. Further research will be necessary to confirm these results. The detection of distant metastases by pretreatment screening worsens the overall survival as compared to distant metastases detected during follow-up.

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Chapter 7

The adverse impact of surveillance intervals on the sensitivity of FDG-PET/CT for the detection of distant metastases in head and neck cancer patients

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Abstract

The presence of distant metastases at initial evaluation influences treatment selection, since no effective systemic treatment for disseminated head and neck squamous cell carcinoma (HNSCC) is currently available. The reported sensitivity for the detection of distant metastases by contrast enhanced (ce)CT and ^{18}F FDG-PET(-CT) differs substantially between studies. We hypothesized that these sensitivity values are highly dependent on the reference standard use, e.g. follow-up term. Therefore, we analyzed our results of ^{18}F FDG-PET-CT (including chest ceCT) with long term follow-up and compared these findings with data from literature, with a particular interest in the different reference standards. Forty-six HNSCC patients with high risk factors underwent pretreatment screening for distant metastases by ^{18}F FDG-PET-CT (including chest ceCT). In 16 patients (35%) distant metastases were detected during screening (6 patients) or during a mean follow-up of 39.4 months (10 patients). The sensitivity and negative predictive value were 83.3 and 97.2% when 6 months, 60.0 and 89.9% when 12 months and 37.5 and 72.2% when 30 months follow-up were used as reference standard, respectively. This is comparable with reported studies with similar reference standards. This critical appraisal on the reference standards used in our and reported studies shows room for improvement for the detection of distant metastases to refrain more patients from unnecessary extensive locoregional treatment for occult metastatic HNSCC.

Introduction

Head and neck squamous cell carcinoma (HNSCC) accounts for approximately 5% of all malignant tumors worldwide. Two-thirds of the patients with HNSCC present with advanced disease. HNSCC preferentially metastasize to regional lymph nodes rather than spread hematogenously. Distant metastases usually occur late in the course of the disease. As results of locoregional treatment have improved significantly over the last decades, more patients are at risk to develop second primary tumours and distant metastases (1).

The presence of distant metastases at initial evaluation influences the prognosis and thus treatment selection: since no effective systemic treatment for disseminated HNSCC is currently available, patients with distant metastases are generally not considered curable and often receive only palliative treatment (2). Therefore, screening for distant metastases is important to avoid futile treatments with extensive burden to patients and high costs.

The reported prevalence of clinically identified distant metastases in HNSCC at presentation is generally considered too low to warrant routine screening for distant metastases in all HNSCC patients. The risk of hematogenous spread is directly related to the stage of disease, particularly to the presence and extent of lymph node metastases, and locoregional control. The yield of screening for distant metastases depends on the applied diagnostic methods (3). High-risk factors have been identified and validated: ≥ 3 lymph node metastases, bilateral lymph node metastases, lymph node metastases ≥ 6 cm, low jugular lymph node metastases, regional recurrence and second primary tumours (4-7). Using these selection criteria, distant metastases were detected in 29-45% of the patients during initial screening (18-19%) or within 12 months follow-up (11-14%) (4-7). Unfortunately, 20% of these high-risk patients who had a negative contrast enhanced CT (ceCT) of the chest at presentation developed distant metastases within 12 months after therapy with curative intent. In one-third of the cases, these missed distant metastases were extrathoracic.

We and others (8) have shown that adding ^{18}F FDG-PET to contrast-enhanced chest CT improves the accuracy and yield of staging, yielding a sensitivity of 63% with a horizon of 12-month follow-up in a prospective multi-center study (6). However, still 15% of these high-risk patients who had a negative chest CT and whole body ^{18}F FDG-PET at presentation developed distant metastases within 12 months after therapy with curative intent (8). Since in almost half of the patients the presence of distant metastases was missed, room for improvement remains. New developments like the integrated combination of ^{18}F FDG-PET and CT (^{18}F FDG-PET/CT) may improve the detection of (occult) distant metastases.

A meta-analysis on integrated ^{18}F FDG-PET/CT showed for the detection of distant metastases and second primary cancers in head and neck cancer patients a pooled sensitivity of 89% and a specificity of 95% (9). However, there was a striking range of sensitivity values (Table 1) (5,6,8,12-18). In previous studies with a long-term follow-up, we reported

a sensitivity of only 55-63% (6,19). Therefore, we analyzed our results of ^{18}F FDG-PET/CT (including chest ceCT) with long-term follow-up and compared these findings with data from the literature, with particular interest in the different reference standards.

Table 1. Clinical studies on detection of distant metastases in HNSCC patients with follow-up as reference standard.

Study	Technique	Patients	N	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Follow-up
Fakhry et al ¹⁷	CT chest	All	37	100	92	86	100	6 months
Krabbe et al ¹⁶	CT chest	All	82	55	63	21	88	>6 months
Brouwer et al ⁵	CT chest	High risk	109	63	86	71	81	12 months
Brouwer et al ⁵	CT chest	High risk LRC	104	73	86	71	87	12 months
Senft et al ⁶	CT chest	High risk	92	37 (24-52)	95 (88-98)	79 (57-91)	75 (66-82)	12 months
Senft et al ⁶	CT chest	High risk LRC	80	50 (33-67)	95 (88-98)	79 (57-91)	83 (75-90)	12 months
Ng et al ^{8**}	CT chest	All	160	50 (30-70)	98 (94-100)	81 (54-96)	91 (85-95)	12 months
Teknos et al ¹³	CT chest	Advanced	12	33	100	100	33	24 months
Krabbe et al ¹⁶	PET	All	149	85	94	58	98	>6 months
Senft et al ⁶	PET	High risk	92	53 (39-67)	93 (86-97)	80 (62-91)	80 (71-86)	12 months
Senft et al ⁶	PET	High risk LRC	80	68 (51-82)	93 (86-97)	79 (61-90)	89 (80-94)	12 months
Ng et al ^{8**}	PET	All	160	77 (56-91)	94.0 (89-97)	71 (51-87)	95.5 (90-98)	12 months
Teknos et al ²⁹	PET	Advanced	12	100	100	100	100	24 months
Haerle et al ¹²	PET/CT	Advanced	299	97	95	67	100	6 months
Fakhry et al ¹⁷	PET/CT	All	37	92	85	73	96	6 months
Gourin et al ¹⁴	PET/CT	All	27	60	95	75	91	12 months
Gourin et al ¹⁵	PET/CT	Recurrent	64	86	84	60	95	
Senft et al ⁶	PET + CT	High risk	92	63 (48-76)	95 (88-98)	86 (70-94)	84 (75-90)	12 months
Senft et al ⁶	PET + CT	High risk LRC	80	82 (65-92)	95 (88-98)	86 (69-94)	93 (86-97)	12 months
Ng et al ^{8**}	PET + CT	All	160	81 (61-93)	99 (95-100)	91 (72-100)	96 (91-99)	12 months
Haerle et al ¹²	PET/CT	Advanced	299	48	94	67	88	30 months@

* mean follow-up; ** distant metastases and second primary tumors; N: Number of patients; LRC: patients with locoregional recurrence and distant metastases during follow-up excluded; 95% confidence intervals between brackets if available. @median follow-up 30 months (range 1-72)

Materials and methods

Patients and study design

We performed a retrospective cohort study on screening for distant metastases with whole body ^{18}F FDG-PET/CT (including chest CE-CT) in high-risk head and neck cancer patients treated at the VU University Medical Center between April 2007 and August 2009. Patients were eligible for screening for distant metastases when meeting the following criteria: (1) HNSCC; (2) candidates for extensive treatment with curative intent (surgery and/or radiotherapy with or without chemotherapy); (3) minimum of 12 months follow-up; in case, no distant metastases were detected; (4) high risk factors for development of distant metastases (7).

HNSCC was histologically confirmed in all cases and all other histological subtypes were excluded. Because of their distinct metastatic patterns squamous cell carcinoma of skin, nasopharynx, nasal cavity and paranasal sinus were excluded. Finally, patients who rejected further workup, patients who died during the first year of follow-up due to other causes than metastatic HNSCC and those who were lost before 1-year follow-up because of other reasons were excluded.

Forty-six patients (33 men and 13 women) with a mean age of 61 years (range 33 – 76) met aforementioned criteria. These patients had the following high risk factors: ≥ 3 lymph node metastases ($n=10$), bilateral lymph node metastases ($n=13$), lymph node metastases of ≥ 6 cm ($n=5$), low jugular lymph node metastases ($n=5$), regional recurrence ($n=7$) and second primary tumours ($n=16$), as assessed by palpation, CT, MRI, and/or ultrasound-guided fine-needle aspiration cytology. Some patients had more than one high risk factor. Primary tumour sites were the oral cavity ($n=14$), oropharynx ($n=16$), hypopharynx ($n=8$) and larynx ($n=11$). Two patients had an unknown primary tumour. Five patients had synchronous second primary tumours. Patients were primary treated by surgery ($n=20$), radiotherapy ($n=8$), chemoradiation ($n=17$) and chemotherapy ($n=1$).

As part of the pretreatment workup, all patients underwent a panendoscopy, ce CT and/or magnetic resonance imaging (MRI) of the head and neck. If considered indicated, fine-needle aspiration of cervical lymph nodes was performed. Post-treatment follow-up was performed by regular visits to the outpatient clinic (every 6-8 weeks in the first year, with increasing intervals in following years). The mean follow-up was 39.4 months (range 1.7-90.2; median 30.2 months). No routine imaging screening for distant metastases was planned during follow-up, but additional examination was performed when suspicion arose either through the patient history or physical examination (e.g. weight loss, lesions/complaints suspicious of recurrence). Six patients developed a locoregional recurrence during follow-up.

¹⁸FDG-PET/CT

All patients underwent ¹⁸FDG-PET/CT pretreatment. During our study period both the Gemini TF-64 and Ingenuity TF integrated PET/CT systems (Philips Medical Systems, Best, The Netherlands) were used to perform whole body (from mid-thighs to skull vertex) ¹⁸FDG-PET/CT scans, followed in the same scan session with ceCT of the chest. Patients fasted for at least 6 hours prior to scanning, which started approximately 60 minutes after intravenous FDG administration. The dose administered was 2.5 MBq/kg body weight ($\pm 10\%$). Glucose levels were checked prior to ¹⁸FDG administration. Low-dose CT was performed with 120kV and 50mAs prior to emission scanning. PET-CT data were reconstructed using a time of flight row-action maximum likelihood algorithm, as implemented by the vendor. Final image matrix size equals 288 x 288 with a voxel size of 2 x 2 x 2 mm. Post-reconstruction image resolution was 5-mm full width at half maximum (FWHM). Preparation and scanning were performed according to the EANM procedure guidelines (10).

The ^{18}F FDG-PET/low-dose CT images were interpreted by experienced nuclear medicine physicians and the ceCT scans by experienced radiologists, concluded with a joint reading session to integrate findings. Readers had access to all relevant clinical information, according to common clinical practice. Most lesions suspicious of being malignant on ^{18}F FDG-PET/CT were confirmed using additional (follow-up) imaging, endoscopic workup and/or biopsy, using a rational approach. In a few cases, findings of ^{18}F FDG-PET/CT were considered unequivocal regarding the presence of distant metastases, and consensus was reached not to perform additional workup by the multidisciplinary team.

Scoring criteria

Radiological criteria for lung metastases were: (multiple) smoothly defined lesions mostly subpleurally located and located at the end of a blood vessel. ^{18}F FDG uptake was considered suspicious for malignancy in case of enhanced uptake incompatible with its physiological bio-distribution. In all patients every scan report (chest ceCT and whole body ^{18}F FDG-PET/CT) was retrospectively scored for suspiciousness of distant metastases using a five point ordinal Likert-scale: 0= no lesion/uptake, 1= definitively benign, 2= probably benign, 3= equivocal, 4= probably malignant and 5= definitely malignant. If more lesions were scored in a single patient, the lesion with the highest score was used for statistical analysis. The Likert scale was reduced to a binominal sensitive scale (0-2= negative, 3-5=positive) and conservative scale (0-3=negative, 4-5=positive) to obtain accuracy data for ceCT and ^{18}F FDG-PET/CT.

Criteria for combined and integrated chest ceCT and ^{18}F FDG-PET/CT reading were based on a previous study (6): positive if PET shows ^{18}F FDG uptake (Likert >0) or if PET shows no uptake and CT is positive (Likert 4 or 5) in small lesions below the detection limit (5 mm) of PET; and negative in all other scorings.

Although the primary goal was screening for distant metastases, we also registered second primary tumours. Patients with second primary tumours outside the head and neck region, which were found during screening, were described separately.

Statistical analysis

^{18}F FDG PET/CT or chest CT findings suspicious of being metastases were considered positive. If no suspicious lesion or lesions suspicious of being either benign or second primary tumours were found, the scan was considered negative. The ^{18}F FDG-PET/CT findings were compared to the findings of further initial workup and findings during follow-up. Negative findings on ^{18}F FDG-PET/CT in patients who developed distant metastases during follow-up were considered as being false-negative, assuming these metastases were (subclinically) present at time of screening.

The result of the clinical diagnostic work-up between screening until a follow-up of 12 months was used as reference standard, and patients were classified as positive or negative with respect to the presence of distant metastases. Other reference standards used were follow-up of 6 months and long term follow-up.

In a separate analysis these results were corrected for locoregional recurrence, since no distinction can be made between growth of subclinical metastases already present at the time of screening and reseeding of a locoregional recurrence after initial screening.

Sensitivity, specificity, positive and negative predictive values of chest ceCT, ¹⁸FDG PET/non ceCT and ¹⁸FDG-PET/ceCT for detection of distant metastases were calculated.

Results

In 22 of the total group of 46 patients (48%) distant metastasis (n=16; 35%) or a second primary tumour (n=6; 13%) was detected during screening or during follow-up after screening. Pretreatment screening identified distant metastases in 6 patients (13%) and a second primary tumour in 1 patient. Distant metastases were located in the lungs (n=14), bone (n=4), liver (n=2) and skin (n=1). In six patients, locoregional recurrence was observed; three of these patients developed distant metastases during follow-up.

Sensitivity, specificity, positive predictive value and negative predictive value of the different imaging modalities, scoring and reference standard are shown in Table 2. By sensitive reading and using a reference standard of 6 months, the sensitivity of ceCT, PET/non ceCT, and PET/ceCT was 67.7, 66.7, and 83.3%, but these figures decreased when a follow-up of 30 months was used to 37.5, 25.0, and 37.5%, respectively.

Table 2. Results of scoring chest CE-CT, whole body FDG-PET/CT and integrated PET/CT and CE-CT using different reference standards (12 and 6 months and median 30.2 months follow-up) and conservative and sensitive reading and reading according Senft et al [6]. LRC: locoregional control (patients with locoregional recurrence and distant metastases during follow-up excluded) ; PPV: positive predictive value; NPV: negative predictive value.

Scoring	Follow-up	Sensitivity %	Specificity %	PPV %	NPV %
CE-CT chest					
Conservative	30 months	18.8 (4.0 - 45.6)	96.7 (82.8 - 99.9)	75.0 (19.4 - 99.4)	69.0 (52.9 - 82.4)
	12 months	23.1 (5.0 - 53.8)	97.0 (84.2 - 99.9)	75.0 (19.4 - 99.4)	76.2 (60.5 - 87.9)
	6 months	33.3 (7.5 - 70.1)	97.3 (85.8 - 99.9)	75.0 (19.4 - 99.4)	85.7 (71.5 - 94.6)
LRC	30 months	23.1 (5.0 - 53.8)	96.7 (82.8 - 99.9)	75.0 (19.4 - 99.4)	74.4 (57.9 - 87.0)
	12 months	30.0 (6.7 - 65.2)	97.0 (84.2 - 99.9)	75.0 (19.4 - 99.4)	82.0 (66.5 - 92.5)
	6 months	67.7 (22.3 - 95.7)	97.3 (85.8 - 99.9)	80.0 (28.4 - 99.5)	94.7 (82.3 - 99.4)
Sensitive	30 months	37.5 (15.2 - 64.6)	83.3 (65.3 - 94.4)	54.5 (23.4 - 83.3)	71.4 (53.7 - 85.4)
	12 months	46.2 (19.2 - 74.9)	84.8 (68.1 - 94.9)	54.5 (23.4 - 83.3)	80.0 (63.1 - 91.6)
	6 months	67.7 (29.9 - 92.5)	86.5 (71.2 - 95.5)	54.5 (23.4 - 83.3)	91.4 (76.9 - 98.2)
LRC	30 months	46.1 (19.2 - 74.9)	83.3 (65.3 - 94.4)	54.5 (23.4 - 83.3)	78.1 (60.0 - 90.7)
	12 months	60.0 (26.2 - 87.8)	84.8 (68.1 - 94.9)	54.4 (23.4 - 83.3)	87.5 (71.0 - 96.5)
	6 months	66.7 (22.3 - 95.7)	81.1 (64.8 - 92.0)	36.4 (10.9 - 69.2)	93.8 (79.2 - 99.2)
PET/CT WB					
Conservative	30 months	18.8 (4.0 - 45.6)	100.0 (88.4 - 100.0)	100.0 (29.2 - 100.0)	70.0 (53.9 - 82.8)
	12 months	30.0 (6.7 - 65.2)	100.0 (88.4 - 100.0)	100.0 (29.2 - 100.0)	83.7 (69.3 - 93.2)
	6 months	50.0 (11.8 - 88.2)	100.0 (88.4 - 100.0)	100.0 (29.2 - 100.0)	93.0 (80.9 - 98.5)
LRC	30 months	23.1 (5.0 - 53.8)	100.0 (88.4 - 100.0)	100.0 (29.2 - 100.0)	75.0 (58.8 - 87.3)
	12 months	30.0 (6.7 - 65.2)	100.0 (88.4 - 100.0)	100.0 (29.2 - 100.0)	82.5 (67.2 - 92.7)
	6 months	50.0 (11.8 - 88.2)	100.0 (88.4 - 100.0)	100.0 (29.2 - 100.0)	92.5 (79.6 - 98.4)
Sensitive	30 months	25.0 (7.3 - 52.4)	90.0 (73.5 - 97.9)	57.1 (18.4 - 90.1)	69.2 (52.4 - 83.0)
	12 months	40.0 (12.2 - 73.8)	91.7 (77.5 - 98.2)	57.1 (18.4 - 90.1)	84.6 (69.5 - 94.1)
	6 months	66.7 (22.3 - 95.7)	92.5 (79.6 - 98.4)	57.1 (18.4 - 90.1)	94.9 (82.7 - 99.4)
LRC	30 months	30.8 (9.1 - 61.4)	90.0 (73.5 - 97.9)	57.1 (18.4 - 90.1)	75.0 (57.8 - 87.9)
	12 months	40.0 (12.2 - 73.8)	90.9 (75.7 - 98.1)	57.1 (18.4 - 90.1)	83.3 (67.2 - 93.6)
	6 months	66.7 (22.3 - 95.7)	81.9 (78.1 - 98.3)	57.1 (18.4 - 90.1)	94.4 (81.3 - 99.3)
PET/CT and chest CT					
According Senft ⁶	30 months	37.5 (15.2 - 64.6)	86.7 (69.3 - 96.2)	60.0 (26.2 - 87.8)	72.2 (54.8 - 85.8)
	12 months	60.0 (26.2 - 87.8)	89.9 (73.9 - 96.9)	60.0 (26.2 - 87.8)	89.9 (73.9 - 96.9)
	6 months	83.3 (35.9 - 99.6)	87.5 (73.2 - 95.8)	50.0 (18.7 - 81.3)	97.2 (85.5 - 99.9)
LRC	30 months	46.1 (19.2 - 74.9)	86.7 (69.3 - 96.2)	60.0 (26.2 - 87.8)	78.8 (61.1 - 91.0)
	12 months	60.0 (26.2 - 87.8)	87.9 (71.8 - 96.6)	60.0 (26.2 - 87.8)	87.9 (71.8 - 96.6)
	6 months	60.0 (26.2 - 87.8)	87.9 (71.8 - 96.6)	60.0 (26.2 - 87.8)	87.9 (71.8 - 96.6)

Discussion

For the detection of distant metastases in HNSCC patients chest CT and whole body ^{18}F FDG-PET are the most important diagnostic imaging techniques. However, studies are difficult to compare and the real value is difficult to assess because of methodological differences. Unfortunately, some studies in head and neck cancer include tumour types other than HNSCC (e.g. nasopharyngeal carcinoma and salivary gland tumours) or sites with different clinical behavior (e.g. nasopharynx, nasal cavity and paranasal sinus) and heterogeneous disease stages. The incidence of distant metastases (depending on type and stage) may influence predictive values of tests. Even more important is the reference standard used. Distant metastases that appear during follow-up in patients who achieved locoregional control must have arisen from subclinical distant spread already present at the time of treatment. Thus, if patients with locoregional disease control develop distant metastases despite negative screening, these distant metastases were missed (below the detection limit) by the technique used for screening. The best references are long-term follow-up and autopsy. The longer the follow-up, the higher the chance that occult distant metastases become manifest and the sensitivity and negative predictive value are expected to decrease. Spector et al (11) performed a retrospective study on 170 patients who developed distant metastases: only 16.5% of patients had distant metastasis at presentation and the remaining patients were diagnosed with distant metastases at a median of 324 days from HNSCC diagnosis (11). In the study of Haerle et al (12) the median time before metachronous (>6 months after screening) distant metastases become manifest was 11 months (range 7-34 months). Thus, only half of the missed or metachronous distant metastases will be diagnosed within 12 months follow-up. In this study the median follow-up was 30.2 months. The number of clinical studies with a clearly defined follow-up as reference standard is limited (Table 1).

Brouwer et al (5) reported on 109 HNSCC patients with risk factors for distant metastases who underwent pretreatment screening by chest CT. Distant metastases were detected in 19% of these patients. Despite negative screening with chest CT, 9 (11%) patients developed distant metastases within a 12 months follow-up period. Using a follow-up of 12 months as reference standard and excluding patients with locoregional recurrence and distant metastases during follow-up, the sensitivity and specificity of the chest CT for the detection of distant metastases were 73% and 86%, respectively (5). This is comparable with the sensitivity of 60% and specificity of 84.8% found in the present study. Using the same risk factors to select patients for screening also the predictive values are comparable.

In a multi-center prospective study of Sent et al. (6), 92 patients with the same high-risk factors as used in this study (33% developed distant metastases), underwent screening for distant metastases by chest CT and whole body ^{18}F FDG-PET. Using a reference standard of 12-months follow-up, the sensitivity, specificity, positive predictive value, and negative predictive value were for chest CT 37, 95, 79 and 75%, for ^{18}F FDG-PET 53, 93, 80,

and 80% and for the combination (visual correlation) of chest and ^{18}F FDG-PET 63, 95, 86, and 84%, respectively. These figures improved when patients who developed distant metastases and locoregional recurrences simultaneously during follow-up were excluded, because no distinction can be made between growth of subclinical metastases already present at the time of screening and reseeding of a locoregional recurrence after initial screening: for chest CT 50, 95, 79 and 83%, for ^{18}F FDG-PET 68, 93, 79, and 89% and for the combination (visual correlation) of chest CT and ^{18}F FDG-PET 82, 95, 86, and 93%, respectively (6).

Xu et al (9) performed a meta-analysis on the accuracy of whole body ^{18}F FDG-PET/CT in staging of head and neck cancer. For the staging of head and neck cancer other than nasopharyngeal cancer a pooled sensitivity and specificity of 88.8% [95% confidence interval (CI): 80.3-94.5] and 93.3% [95% CI: 91.0-94.5%], respectively, were found for ^{18}F FDG-PET/CT. The diagnostic value of ^{18}F FDG-PET/CT was not significantly better than PET only (9).

Teknos et al (13) compared chest CT and PET in 12 consecutive advanced stage HNSCC patients. Distant metastases were detected by FDG-PET in 3 patients and by CT in 1 of those 3 patients. During follow-up of 24-28 months in no other patients distant metastases became manifest (13).

In 27 untreated HNSCC patients with mainly advanced HNSCC and 19% distant metastases Gourin et al (14) reported for the detection of distant metastases by ^{18}F FDG-PET/CT a sensitivity of 100%. However, when 12 months follow-up was used as reference standard the sensitivity decreased to 60% and specificity, positive predictive value and negative predictive value were 95%, 75% and 91%, respectively (14). In a later study of the same group (15) in 64 patients with suspected recurrent HNSCC following definitive treatment the incidence of distant metastases was 23%. Using a reference standard of 12 months follow-up the sensitivity, specificity, positive predictive value and negative predictive value for the detection of distant metastases by ^{18}F FDG-PET/CT were 86%, 84%, 60% and 95%, respectively (15). The higher sensitivity and lower specificity in this second group are suggestive for a more sensitive reading.

Krabbe et al (16) reported on screening for distant metastases by ^{18}F FDG-PET in 149 HNSCC patients. In thirteen (8.7%) of these patients distant metastases were detected during screening or follow-up of at least 6 months. Using this follow-up as the reference standard, a sensitivity of 85% and a specificity of 93% for ^{18}F FDG-PET were found. In the subgroup of 82 patients who underwent ^{18}F FDG-PET and chest ceCT these figures were 82% and 92% for ^{18}F FDG-PET, compared to 55% and 63%, respectively, for chest ceCT (16).

Ng et al (8) compared the detection of distant malignancies (distant metastases and second primary tumours) by ^{18}F FDG-PET and extended-field CE-CT in 160 newly diagnosed oropharyngeal and hypopharyngeal squamous cell carcinoma patients with negative results from chest radiography, liver ultrasound and bone scanning, with a follow-up of 12 months. Twenty-six (16.3%) of these patients developed distant malignancies. The percentages of additionally detected distant malignancies by ^{18}F FDG-PET and ceCT were

12.5% and 8.1%, respectively. The sensitivity of ^{18}F FDG-PET was significantly higher (76.9% vs. 50.0%), while its specificity was slightly lower (94.0% vs. 97.8%) than ceCT. Visual correlation of ^{18}F FDG-PET and CT improved the sensitivity and specificity to 80.8% and 98.5%, respectively, leading to alteration of treatment in 13.1% of patients (8).

Haerle et al (12) reported on 299 patients with advanced stage HNSCC who underwent screening for distant metastases using ^{18}F FDG-PET/CT. PET/CT detected distant metastases in 29 (10%) patients, while in 30 (11%) patients distant metastases were diagnosed during a median follow-up of 30 months (range 1-72 months). A sensitivity of 97% and a specificity of 95% were reported using a reference standard of 6 months. When long-term follow-up was used as reference standard the sensitivity decreased to 48% (12).

Recently, Suenaga et al. (18) reported on 170 patients previously treated for HNSCC with suspected recurrence who underwent PET/CT, consisting of non-ceCT and ceCT. In 8,8% of the patients, distant metastases were detected during screening or follow-up of at least 12 months. The sensitivity and specificity for chest ceCT were 33 and 99%, for PET/CT with non-ceCT 53 and 99%, and for PET/CT with ceCT 60 and 99%, respectively. They concluded that the added value of ceCT at ^{18}F FDG-PET/CT is minimal. Statistically not significant and likely not clinically relevant (18).

In 37 HNSCC patients scheduled for salvage surgery after chemoradiation Fakhry et al (17) performed screening for distant metastases by chest ceCT and whole body ^{18}F FDG-PET/CT. In 9 (24%) patients distant metastases were found. Using a follow-up of at least 6 months as reference standard no false negative findings were observed. The sensitivity, specificity, positive predictive value and negative predictive value of were for chest CT 100%, 94%, 86% and 100% and for PET/CT 92%, 87%, 74% and 97%, respectively (17).

From the reported studies it can be concluded that the specificity, positive predictive value and negative predictive value for chest CT and whole body PET(/CT) are generally high. In the reported studies, when the follow-up (as reference standard) increased from 6, to 12 and to 24 months the sensitivity for chest CT decreased from 100%, to 37-73% and to 33% respectively and for the combination of PET and CT (visually correlated and integrated) from 92-97%, to 63-82% and to 48% (30 months).

In this study, the accuracy was determined using the different reference standards in the same cohort of patients. The results of these analyses confirm the results found in the comparison between the reported studies. This is illustrated by the sensitivity of the combination of chest ceCT and ^{18}F FDG-PET/CT of 60-83% after 6 months follow-up, 60% after 12 months follow-up and 38-46% after a median follow-up of 30.2 months. When only patients with locoregional control during surveillance were analyzed the sensitivity increased up to 23%. In this study sensitive reading improved the sensitivity up to 34% for CT and up to 17% for PET/CT, while the specificity decreased but remained high.

Now the question arises if for pretreatment screening for distant metastases these diagnostic techniques are sufficient enough? When it is the physicians' opinion that an interval between HNSCC diagnosis and manifest distant metastases of at least 12 months

justifies extensive locoregional treatment (20), one could argue that the sensitivity of 60-82% for the combination of PET and chest CT may be acceptable. Then, in future studies 12 months follow-up as reference standard will be sufficient. Nevertheless, this critical appraisal on the reference standards used in the reported studies shows room for improvement for the pretreatment detection of distant metastases.

Due to the introduction of multi-channel receiver MRI, whole body MRI has become clinically feasible, with substantially reduced examination times (21) Chan et al (22) reported on 103 untreated oro- and hypopharyngeal carcinoma patients who underwent screening using ^{18}F FDG-PET-CT and WB-MRI. Distant metastases ($n=8$) or second primary tumors ($n=10$) were detected in 18 (17.5%) patients. Using a follow-up of at least 12 months as a reference standard, the sensitivity, specificity, positive and negative predictive values of WB-MRI were 67%, 96%, 80% and 93%, respectively. The figures for PET-CT were 83%, 95%, 79% and 96%, respectively. For combined reading these figures were 78%, 98%, 88% and 95%, respectively. The diagnostic capability of PET-CT seems higher, but this difference was statistically non-significant. Technical improvements like diffusion-weighted whole body imaging with background-body-signal-suppression (DWIBS) and experience in whole body MRI may increase the accuracy of this technique. With the rising concern of radiation dose in medical imaging, WB-MRI may be considered as a replacement for PET-CT for the whole body screening of patients. However, at the moment, none of these new methods have proved to be better for this topic. With the introduction of PET-MRI fusion studies, combined readings may improve the detection of distant metastases in the near future.

In conclusion, for pretreatment screening on distant metastases in HNSCC patients with high-risk factors, ^{18}F FDG-PET/ceCT should be performed. The reported accuracy, particularly sensitivity, of chest CT, ^{18}F FDG-PET/non-ceCT, and ^{18}F FDG-PET/ceCT for the detection of distant metastases is highly dependent on the reference standard used. A reference standard of 12 months may be sufficient, although still only half of the subclinical distant metastases missed during initial screening will become manifest within this time period. There is room for better diagnostic screenings techniques to refrain more patients from unnecessary extensive locoregional treatment for occult metastatic HNSCC.

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Chapter 8

Pretreatment screening for distant metastases in the Dutch head and neck centers: 10 years later

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Abstract

To evaluate the current practice and change in practice concerning screening for distant metastases in head and neck squamous cell carcinoma patients, we performed a survey with the same questionnaire as 10 years ago among the eight centers of Dutch Head and Neck Society treating head and neck cancer in The Netherlands. Factors related to extensive lymph node metastases are the most frequent indication for screening for distant metastases. The combinations of whole body ^{18}F FDG-PET-CT and contrast enhanced chest CT are nowadays the diagnostic techniques for routinely screening for distant metastases. Screening for distant metastases is performed more frequently than 10 years ago. Although the sensitivity of the diagnostic pathway needs to be improved, most centers are satisfied with the current diagnostic pathway. A reduction of variation in indications and diagnostic techniques used for screening for distant metastases is observed during the last 10 years. In future guidelines patients' selection and diagnostic tests need to be specified in more detail.

Introduction

Head and neck squamous cell carcinomas (HNSCC) have a tendency to metastasize to regional lymph nodes rather than to spread hematogeneously to distant sites. The incidence of distant metastases is directly related to the stage of the tumour, particularly the presence and extension of lymph node metastases, and regional control above the clavicles. Once distant metastases have been detected, the prognosis is dismal. The median time to death from the diagnosis of distant metastases ranges from 1 to 12 months. About 88% of patients with distant metastases will die within 12 months. Thus, the detection of distant metastases is critical for prognostication and for the choice of treatment in patients with HNSCC. Patients with known distant metastatic disease can possibly be spared the toxicities of aggressive and often unnecessary locoregional therapy (1).

Ten years ago we performed a survey which showed a substantial variation in indications and diagnostic techniques used for pretreatment screening for distant metastases between the major institutions treating head and neck cancer in The Netherlands. Eight of 19 (42%) clinicians stated that they were not satisfied with the current course of diagnostic investigations, because of a perceived lack of sensitivity of the current tests (2). In these 10 years diagnostic techniques improved and PET-CT became wider available.

Since then an update of the Dutch guidelines on laryngeal carcinoma (version 3.0, 2010) of the Dutch Head and Neck Society (NWHHT) was published (oncoline.nl) in which it was stated that screening by chest CT was indicated in patients with three or more lymph node metastases, low jugular metastases and N2c or N3 disease. In the recent version of the Dutch NWHHT guidelines for head and neck cancer it is advised to perform ¹⁸FDG-PET-CT in high risk HNSCC patients.

To evaluate the current practice and change in practice concerning the diagnostic work-up in HNSCC patients, we performed a survey with the same questionnaire as 10 years ago among the 8 centers of the Dutch Head and Neck Society treating head and neck cancer in The Netherlands.

Material and methods

The questionnaire on current clinical practice concerning screening for distant metastases in HNSCC patients was sent to eight head and neck surgeons as representatives of the eight head and neck centers of the Dutch Head and Neck Society (NWHHT) treating head and neck cancer in The Netherlands. The questionnaire (Figure 1) was accompanied by an explanatory mail.

Questionnaire on current practice concerning diagnostic work-up

Q. 1: What indications do you use to screen for distant metastases in patients without specific complaints or symptoms and with a normal X-thorax and blood tests?
(more than 1 answer allowed)

- ☐ T-stage 3-4
- ☐ advanced N-stage, i.e.:.....
- ☐ localisation of lymph nodes in the neck, i.e.:.....
- ☐ surgical intervention for a local recurrence
- ☐ surgical intervention for a second primary HNSCC
- ☐ extremely mutilating surgical intervention

- ☐ clinically 3 or more lymph node metastases
- ☐ low jugular lymph node metastases
- ☐ bilateral lymph node metastases
- ☐ metastases of 6 cm or larger
- ☐ local recurrence
- ☐ regional recurrence
- ☐ second primary head and neck cancer
- ☐ radiological extra nodal spread

- ☐ none, I never screen
- ☐ other, i.e.:.....

Q. 2: When you decide to perform screening, which technique(s) do you use?
(more than 1 answer allowed)

- ☐ none, I never screen
- ☐ X-thorax
- ☐ CT scan of the thorax
- ☐ ultrasound of the liver
- ☐ CT scan of the liver
- ☐ bone scintigraphy
- ☐ PET scan

- ☐ PET-CT (low dose CT)
- ☐ PET-CT (diagnostic contrast enhanced CT)
- ☐ Whole body MRI

- ☐ other, i.e.:

Q. 3: How many times a year is screening for distant metastases performed in your hospital?

- ☐ 0 times
 - ☐ 1-10 times
-

- 11-20 times
- > 20 times, i.e.:.....

Q. 4: In a patient who is being considered for a extensive surgical intervention, when would you decide not to perform this surgery, but to treat the patient palliatively?

- If I would know that distant metastases would become clinically evident within 3 months after treatment
- If I would know that distant metastases would become clinically evident within 3 to 6 months after treatment
- If I would know that distant metastases would become clinically evident within 6 to 12 months after treatment
- If I would know that distant metastases would become clinically evident within 12 to 24 months after treatment

Explanation -

What we intended with this question was to name a subtle distinction in this dilemma: if you want to treat a patient with curative surgery for, for example, a T3N1 oropharyngeal carcinoma, but preoperatively this patient turns out to have distant metastases, most surgeons will refrain from surgery and choose for a palliative treatment. On the other hand, when distant metastases become clinical evident after 2 years, nobody will regret having performed surgery.

We wanted to find out where the subtle distinction between operating and refraining from surgery lies.

Q. 5: Are you satisfied with the current diagnostic pathway?

- yes
- no, because.....

Results

The response rate was 100%. Indications for screening for distant metastases are summarized in Table 1. In Table 2 indications for screening for distant metastases related to lymph node metastasis were specified. In one center all N+ patients undergo screening for distant metastases. The results of the question which techniques (besides chest X-ray) are routinely used for screening are shown in Table 3

Table 1. Results relating to question about indications for screening for distant metastases

Indication	Responders		Specifications	
	2005 (n=19)	2015 (n=8)	2005	2015
Lymph node metastasis	12/19 (63%)	8/8 (100%)	≥ N2b, levels, IV- V, supraclavicular	
Extremely mutilating surgical intervention	11/19 (58%)	5/8 (63%)		
Local and/or regional recurrence	9/19 (47%)	4/8 (50%)		
T-stage 3-4	6/19 (32%)	1/8 (13%)		
Second primary head and neck cancer	4/19 (21%)	3/8 (38%)		

Table 2. Indications for screening for distant metastases related to lymph node metastasis.

Indication	Responders (n=8)
Advanced N-stage (N2-N3)	5* (63%)
Localisation of lymph nodes in the neck (Level V)	4 (50%)
Clinically 3 or more lymph node metastases	6 (75%)
Low jugular lymph node metastases	7 (88%)
Bilateral lymph node metastases	7 (88%)
Metastases of 6 cm or larger	8 (100%)
Regional recurrence	3 (38%)
Radiological extra nodal spread	2 (25%)

*In one center not N2a

Table 3. Results relating to question which techniques are routinely used besides chest X-ray.

Diagnostic technique	Responders	
	2005 (n=19)	2015 (n=8)
Contrast enhanced chest CT	16/19 (84%)	7/8 (88%)
Ultrasound liver	10/19 (53%)	
CT liver	3/19 (16%)	
Bone scintigraphy	8/19 (42%)	
PET(-low dose CT)	13/19 (68%)*	8/8 (100%)**

*Only in research protocol

** In one center only in selected cases

Two (25%) clinicians reported screening in 11 to 20 patients annually and 6 (75%) performed screening for distant metastases in more than 20 patients.

If a patient with HNSCC could only be cured by extensive surgery, the number of clinicians that would have refrained from curative surgery and resorted to palliative measures if they considered that the patient would develop distant metastases, within a certain period was 7 (88%) for distant metastases within 3 months after surgery, 7 (88%) for 3 to 6 months, 6 (75%) for 6 to 12 months and 2 (25%) for 12 to 24 months after surgery. One center could not answer this question because it “depends on many factors like actual complaints caused by the tumor, co-morbidity, patient preferences, expected functional outcome of the procedure, etc”.

Six (75%) centers were satisfied with the current diagnostic pathway. Two (25%) centers stated that they were not satisfied with the current course of diagnostic investigations, because “Dilemma between routinely performing chest X-ray or CT (in head and neck cancer patients in general)” and “Financial problems (like to do more chest CT and/or PET-CT)”.

Discussion

In ten years' time the clinical practice of screening for distant metastases has been changed: extensive lymph node metastases is the main indication for pretreatment screening of distant metastases, ¹⁸FDG-PET-CT combined with contrast-enhanced chest CT is the current screening technique and most centers are satisfied with current diagnostic pathway.

The incidence of distant metastases from HNSCC at presentation is generally too low to warrant routinely extensive radiological screening for distant metastases in all HNSCC patients. Therefore, high risk factors have been identified and validated: three or more lymph node metastases, bilateral lymph node metastases, lymph nodes larger than 6 cm, low jugular lymph node metastases, regional tumour recurrence and second primary tumours (3,4). Another radiological high risk factor is extra nodal spread (5). Most of the centers use these criteria, although some centers simplified these factors by using N2-N3 disease as indication for screening for distant metastases. Some indications do not harbor a high risk of distant metastases, but may be justified if the morbidity of a planned treatment or burden to the patient is very high, e.g., extremely mutilating surgery.

While 10 years ago several diagnostic techniques were used, currently PET-CT and contrast enhanced chest CT are the only techniques and are used in almost all centers routinely. This combination of PET-CT and contrast-enhanced chest CT is the best strategy to screen for distant metastases (6,7). In a meta-analysis Xu et al (8) found for integrated PET-CT a pooled sensitivity and specificity to detect distant metastases of 88% and 95%, respectively. However, about half of the high risk patients develop distant metastases during follow-up, despite negative screening by PET-CT. Therefore, room for improvement remains. Due to technical improvement whole body MRI is feasible (9) and studies in these high risk HNSCC patients comparing this new technique with the current best technique, i.e. PET-CT (including contrast enhanced chest CT), are needed.

All centers would refrain from extensive treatment if a HNSCC patient would develop clinically manifest distant metastases within 6 months, except one center which makes the decision to treat with curative intent dependent on many factors like actual complaints caused by the tumour, co-morbidity, patient preferences and expected functional outcome of the procedure. Almost all centers would only offer treatment with curative intent if development of distant metastases are expected not to be within 12 months.

Pretreatment screening for distant metastases is performed more frequently: 75% of head and neck centers more than 20 times a year, in comparison with 26% of clinicians 10 years ago. Ten years ago 42% of the clinicians stated that they were not satisfied with the course of diagnostic investigations, because of a perceived lack of sensitivity of the tests at that moment. Although nowadays the sensitivity of the best diagnostic technique, i.e. PET-CT, is still limited, none of the centers mentioned to be dissatisfied by the performance of the diagnostic tests. One center was not satisfied because of the dilemma to

perform routinely chest X-ray or CT. However, plain chest X-ray films detect only a minority of all malignant pulmonary lesions detected by CT. Another center has financial problems with this diagnostic pathway, because the physicians like to do more chest CT and/or PET-CT. Although ^{18}F FDG-PET is an expensive diagnostic test, the detection of distant metastases can avoid futile expensive treatments and therefore did not lead to additional costs. When applied in the pre-treatment work-up of high risk HNSCC the addition of ^{18}F FDG-PET did not lead to additional costs (10). Moreover, PET-CT is nowadays commonly used for radiation treatment planning.

Through the response rate of 100% and the centralized care for head and neck cancer patients the clinical practice the entire Netherlands is covered by this survey. The same questionnaire as 10 years ago was used making comparison possible.

In the previous survey individual physicians from all eight centers instead of one representative per center were asked limiting direct comparison between both surveys to some extent.

This survey shows a reduction of variation in indications and diagnostic techniques used for screening for distant metastases between the Dutch centers treating head and neck cancer in The Netherlands over the last 10 years. Although the sensitivity of ^{18}F FDG-PET-CT is limited the physicians in most centers are satisfied with the policy to screen HNSCC patients with extensive lymph node involvement routinely by whole body ^{18}F FDG-PET-CT and contrast-enhanced chest CT. In future guidelines patients' selection and diagnostic tests need to be specified in more detail.

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Chapter 9

General discussion and future perspectives

Distant metastases (DM) are defined as tumour spread to other organs. Lung, liver, and bone are the most common sites for hematogenous metastases of head and neck squamous cell carcinoma (HNSCC). The incidence of distant metastasis in HNSCC is low for the general HNSCC population: generally below 5% at presentation [1]. HNSCC patients with DM are generally candidates for palliative treatment scenarios only, because currently no systemic therapy has curative potential in HNSCC patients with distant disease [2] and extensive locoregional treatment is usually considered futile in these patients. Therefore, pretreatment screening for DM is currently performed mainly to avoid unnecessary extensive locoregional treatments. Examinations to detect DM can also be performed during follow-up as screening in patients with no symptoms, or if symptoms suggestive of DM are observed after completion of locoregional treatment. However, as patients with DM often receive only supportive care or treatment aimed at relief of symptoms, the use of screening for asymptomatic DM post treatment is questionable [3].

Until recently the role of performing aggressive treatment of distant sites of disease was arguably more controversial given its questionable therapeutic benefit [2]. However, the concept of treating oligometastases, successful for some other neoplasms, has been reintroduced in HNSCC and may change the treatment paradigm. If locoregional disease (if still present) is controlled, or resected, and the distant sites are ablated (surgically or with radiation), a prolonged disease-free interval, and possible cure, may be achieved. Treatment options for solitary or a very limited number of isolated well-defined metastatic lesions, which are most frequently located in the lungs, are metastatectomy or stereotactic body radiotherapy (SBRT). Highly selected patients treated by these modalities for limited distant metastatic disease may have long-term disease-free survival.

Nevertheless, the decision to consider intervention for proven or highly suspected distant metastatic disease, particularly for multiple lesions, must be highly individualized [4]. As tobacco use and excessive alcohol consumption are major risk factors for development of HNSCC [5], these patients often suffer from primary neoplasm in other locations such as lung or esophagus. In patients with a solitary pulmonary lesion, it is often difficult to radiologically differentiate a second primary lung tumour from metastatic disease. However, surgery and stereotactic radiotherapy may be successful both in primary lung cancer and oligometastases to the lungs. A systematic review and meta-analysis revealed that pulmonary metastatectomy for metachronous pulmonary metastases from HNSCC is effective and may offer prolonged survival for selected patients [6]. Moreover, if more effective systemic treatments become available, more patients may benefit from screening for DM during follow-up as well.

If patients with poor performance status are not candidates for systemic therapy, these patients may not benefit from screening for distant metastases during follow-up. Therefore, in screening during follow up the focus should be on patients with good performance status, e.g. generally patients with HPV-related HNSCC.

Imaging techniques to detect DM

FDG PET/CT

Because the vast majority of HNSCC patients with DM suffer from pulmonary metastases it could be argued that an examination of the chest, e.g. chest computed tomography (CT), would be sufficient to identify patients with DM for whom extensive locoregional treatments would be futile [7]. However, if patients with oligometastases are considered for treatment with curative intent, information about the overall distant metastatic load is of importance and can only be assessed by a whole body screening technique such as ^{18}F -fluoro-2-deoxy-D-glucose positron emission tomography (^{18}F FDG-PET). For HNSCC patients with high-risk factors for DM, the combination of ^{18}F FDG-PET and chest CT is not associated with additional cost [8]. Senft et al [9] screened 92 HNSCC patients with high risk factors [10] for DM (incidence 33%; 30 patients) and found that using a follow-up of 12 months as a reference standard, the addition of whole body ^{18}F FDG-PET to chest CT increased the sensitivity from 37% [false negative rate (FNR) 25% and false positive (FPR) 21%] to 63% (FNR 16% and FPR 14%) [9]. Ng et al [11] reported that for the detection of DM and second primary tumours in 160 newly diagnosed oropharyngeal and hypopharyngeal squamous cell carcinoma patients with negative results from chest radiography, liver ultrasound and bone scan with a minimum follow-up of 12 months as reference standard (incidence 16%; 26 patients), the addition of ^{18}F FDG-PET to chest CT resulted in an increased sensitivity from 50% (FNR 9% and FPR 19%) to 81% (FNR 3% and FPR 9%) [11]. In a prospective cohort study of 307 HNSCC patients trying to determine the detection rate of distant metastasis and synchronous cancer comparing clinically used imaging strategies based on a) chest X-ray plus head and neck magnetic resonance imaging and b) chest computed tomography plus head and neck MRI to c) ^{18}F FDG-PET/CT, it was found that a clinical imaging strategy based on ^{18}F FDG-PET/CT demonstrated a significantly higher detection rate of distant metastasis and/or synchronous cancer [12]. By virtue of its high spatial resolution, CT may serve as a cross-sectional imaging tool complementary to ^{18}F FDG-PET in the evaluation of DM in HNSCC patients and may help to characterize ^{18}F FDG abnormalities, which may reduce the rate of false positive findings, and consequently, false positives due to inflammatory conditions.

In general, in patients with HNSCC routine extension of ^{18}F FDG-PET/CT scans to include the head and abdomen is only indicated when there is no evidence of thoracic metastases. [13]. However, in HNSCC patients considered to be at high risk for distant metastasis, screening with integrated whole body ^{18}F FDG-PET/CT including a dedicated CT scan of the chest is currently the most valuable screening technique. A meta-analysis of integrated ^{18}F FDG-PET/CT for the detection of DM and second primary cancers in HNSCC patients showed a pooled sensitivity of 89% and a specificity of 95% [14]. However, the striking range of sensitivity values (67-100%) in this meta-analysis seems to be caused by the different reference standards used. In a study by Senft et al [15], if the follow-up (as reference standard) was increased from 6 months to 12 and to 30 months, the sensitivity for

the combination of PET and CT (visually correlated and integrated) decreased from 83-97% to 60-82% and to 38-48%. Comparable figures were found in post-treatment surveillance [16]. When it is the physicians' opinion that an interval between HNSCC diagnosis and the diagnosis of DM at 12 months or more justifies extensive locoregional treatment [17], the sensitivity of 60-82% for the combination of ^{18}F FDG-PET and chest CT may be acceptable. Nevertheless, these figures show room for improvement.

Delayed time-point ^{18}F FDG-PET involves the acquisition of ^{18}F FDG-PET data at a delayed time point after ^{18}F FDG administration, i.e. far beyond 1h post ^{18}F FDG administration as is usual in "standard" ^{18}F FDG-PET. The potential advantage of delayed time-point ^{18}F FDG-PET is increased sensitivity due to continued clearance of background activity, including inflammatory tissue, and continued ^{18}F FDG accumulation in malignant lesions [18,19]. By taking advantage of the difference in the time course of ^{18}F FDG uptake across diverse tissues, the combined early (standard) time-point ^{18}F FDG-PET and delayed time-point ^{18}F FDG-PET may improve distant metastasis detection. Uesaka et al [20] found for the detection of DM in 155 lung cancer patients that dual time-point ^{18}F FDG-PET/CT (60 and 180 min after FDG injection) improved the specificity significantly [20]. To date, there are no published studies that have evaluated delayed time-point ^{18}F FDG-PET for the detection of distant metastasis from HNSCC.

Some have hypothesized that other PET tracers may improve the accuracy of PET [21]. Hoshikawa et al [22] compared the diagnostic efficacy of 3'-deoxy- ^{18}F -fluorothymidine (FLT)-PET with that of ^{18}F FDG-PET regarding second primary cancers and DM in 88 HNSCC patients. FLT was not able to improve the sensitivity of PET when compared to the use of ^{18}F FDG: 78% and 90%, respectively. It was concluded that FLT-PET should not replace ^{18}F FDG PET for pretreatment metastasis staging in HNSCC patients because of its lower sensitivity and higher background activity in the liver and bone marrow [22].

Whole body MRI

As a result of the introduction of multi-channel receiver magnetic resonance imaging (MRI), whole body MRI (WB-MRI) has become clinically feasible, with substantially reduced examination times. Commonly used WB-MRI sequences such as (gadolinium-enhanced) T1-weighted, T2-weighted, and short inversion time inversion-recovery (STIR) imaging allow for the evaluation of anatomic and pathologic changes because of their excellent soft tissue contrast. In addition, a relatively newer WB MRI technique that has gained substantial popularity since its introduction a decade ago, is WB diffusion-weighted MRI (DW-MRI). A potential advantage of WB DW MRI over standard anatomical WB MRI sequences is a higher lesion-to-background contrast which eliminates the need for gadolinium-enhanced sequences [23]. The advantages of WB MRI over ^{18}F FDG-PET/CT are its lower costs and the lack of ionizing radiation, as WB ^{18}F FDG-PET/CT scanning is accompanied by a substantial radiation dose and (secondary) cancer risk. Huang et al estimated that effective dose from WB ^{18}F FDG-PET/CT performed with a 64-detector CT scanner, an administered ^{18}F FDG activity of 370 MBq, was between 13.45 and 32.18 mSv for

different diagnostic CT protocols with the CT component contributing between 54% and 81% of the total combined dose. The cancer risk induced was calculated to be between 0.163% and 0.514% for 20-year-old patients, with a decreased risk when age at exposure increased [24]. In a more recent study Quinn et al reported a mean CT effective dose of 15.4 ± 5.0 mSv and mean ^{18}F FDG-PET/CT effective dose of 24.4 ± 4.3 mSv for diagnostic ^{18}F FDG-PET/CT patients [25]. Furthermore, there is no need for patient preparation, e.g. contrast agents or fasting.

A meta-analysis of the diagnostic value of WB MRI (including DW imaging) for the detection of primary and metastatic malignancies included 13 studies with a total sample size of 1067 patients with various cancers. It was reported that WB MRI had a similar area under the receiver operating characteristic curve [AUC (0.966, 95% CI 0.940-0.992)] compared with that of ^{18}F FDG-PET/CT (0.984, 95% CI 0.965-0.999). These data suggest that both techniques have a similar diagnostic performance in this setting [26]. The feasibility of whole body MRI (including DW imaging) for the evaluation of distant malignancies in HNSCC was demonstrated in 33 patients [27]. Ng et al [28] prospectively evaluated the accuracy of 3.0-T WB-MRI, integrated ^{18}F FDG-PET/CT, and their combined interpretation for the assessment of distant-site status (DM or synchronous tumours) in 150 patients with untreated nasopharyngeal carcinoma (incidence 12%; 18 patients). WB-MRI and ^{18}F FDG-PET-CT showed similar sensitivity (77.8% vs 72.2%), specificity (98.5% vs 97.7%), positive predictive value (87.5% vs 81.3%) and negative predictive value (97.0% vs. 96.3%). Combined interpretation of WB-MRI and ^{18}F FDG-PET/CT showed slightly (not significant) benefit over either technique alone: sensitivity 88.9%, specificity 99.2%, positive predictive value 94.1% and negative predictive value 98.5%. Chan et al. [29] reported on 103 untreated oro- and hypopharyngeal carcinoma patients who underwent screening using ^{18}F FDG-PET/CT and WB MRI. Distant metastases ($n=8$) or second primary tumours ($n=10$) were detected in 18 (17.5%) patients. When a follow-up of at least 12 months as a reference standard, the sensitivity, specificity, positive and negative predictive values of WB MRI were 67%, 96%, 80% and 93%, respectively. The figures for ^{18}F FDG-PET/CT were 83%, 95%, 79% and 94%, respectively. Combined these figures were 78%, 98%, 88% and 95%, respectively. The diagnostic capability of ^{18}F FDG-PET/CT seems higher, but this difference was statistically non-significant [29]. Technical improvements like diffusion-weighted whole body imaging with background body signal suppression (DWIBS) and experience in WB-MRI may increase the accuracy of this technique [24]. With the rising concern over radiation dose in medical imaging, WB-MRI may be considered as a potential replacement for ^{18}F FDG-PET/CT for the whole body screening of patients. With introduction of ^{18}F FDG-PET/MRI fusion studies, combined readings may improve the detection of DM in the near future.

^{18}F FDG-PET/MRI

Since both ^{18}F FDG-PET and MRI have possibilities regarding detection of DM, combined ^{18}F FDG-PET/MRI may further improve detection of DM. Images obtained with the ^{18}F FDG-

PET-MRI system exhibited better detailed resolution and greater image contrast in comparison to those from the ^{18}F FDG-PET/CT system. However, combining the two advanced imaging technologies without degrading the original optimum performance of either is challenging [30]. Heusch et al [31] found no significant difference between ^{18}F FDG PET/MRI and ^{18}F FDG PET/CT in detection of DM in 42 consecutive patients with different histologically confirmed solid primary malignant tumours: sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy were 50 %, 82 %, 40 %, 88 % and 76 % for ^{18}F FDG-PET/CT and 50 %, 91 %, 57 %, 89 % and 83 % for ^{18}F FDG-PET/MRI (incidence 21%: 9 patients)[31]. Similarly, in a pilot study of only 14 patients with head and neck cancer, ^{18}F FDG-PET/MR imaging and ^{18}F FDG-PET/CT seem to provide comparable results in detection of lymph node and DM [32]. It seems that ^{18}F FDG-PET/MRI also bears a comparable accuracy to ^{18}F FDG-PET/CT in characterization of incidental tracer uptake [33]. However, it is likely that as a result of the low level of experiences at the present time the ^{18}F FDG-PET/MRI protocols will be improved. ^{18}F FDG-PET/MR imaging is not associated with radiation for attenuation correction.

Selection of patients to undergo screening for DM

The reported prevalence of clinically identified DM in HNSCC patients at presentation varies from 4% to 24% and is too low to warrant routine screening of all HNSCC patients. To increase the yield of examinations for the detection of DM, patients with high risk factors should be selected for screening for DM (Table 1) [3]. Although ^{18}F FDG-PET is an expensive diagnostic test, detection of DM avoids futile expensive treatments. The use of ^{18}F FDG-PET/CT did not lead to additional costs in pretreatment screening for DM as compared to chest CT in 80 HNSCC patients with the following identified and validated clinically high risk factors [10]: More than 3 lymph node metastases, bilateral lymph node metastases, lymph node metastases of 6 cm or larger, low jugular lymph node metastases, regional recurrence and second primary tumors [8]. When these high risk factors were used, the prevalence of DM was 44% [10]. High risk factors, such as radiologically determined extranodal spread and matted nodes increase the prevalence of DM even further [34], whereas SUV of the primary tumor and lymph node metastases were not predictive for the development of DM in these high risk HNSCC patients [35]. Because whole body MRI is a non-ionizing and less expensive technique compared with ^{18}F FDG-PET/CT, it can be anticipated that it will become acceptable for use in screening patients with a lower risk of DM. Several studies identified other risk factors for the development of DM.

Clinical and histopathological parameters

Leemans et al [35] reported on the development of DM in 281 patients who underwent neck dissection and had locoregional control during follow-up. Patients with histologically

proven lymph node metastasis had twice the incidence of DM compared to those who had not [13.6% vs. 6.9%]. Patients with more than three histologically positive lymph nodes were at highest risk for development of DM (46.8%). The presence of histologically determined extranodal spread was associated with a threefold increase in the incidence of DM, as compared to patients without this feature (19.1% vs. 6.7%) [36]. Coca-Pelaz et al. [37] analyzed risk factors for the development of DM in 443 patients with surgically treated primary HNSCC. Patients with poorly differentiated tumours [hazard ratio (HR) 3.73], multiple (three or more nodes; HR 3.63), or bilateral nodal metastases (HR 7.06) were at greater risk of DM [37]. Duprez et al. [38] recently reported that N-stage (N1 5.1% vs N4 28.9%), stage grouping (stage I 1.2% vs. stage IV 18.0%), extranodal spread (32.0% vs. 11.9%), tumour site (i.e. hypopharynx), locoregional residual disease (24% vs 10%), locoregional recurrence (29% vs. 10%) and for oropharyngeal cancer an HPV-negative status (5-year distant control rate 91% vs. 70%) were risk factors for DM [38]. León et al [39] analyzed the development of DM in 1244 patients with oral cavity, pharyngeal, or laryngeal squamous cell carcinomas with locoregional control and found that 86% of the DM appeared within the first 2 years after diagnosis of the primary tumour, and the factors that were independently associated with the risk of DM were regional extension (N), local extension (T), and location of the tumour in the hypopharynx and supraglottis [39]. Among nasopharyngeal carcinoma patients, only those with Epstein-Barr virus positivity [odds ratio (OR) 3.1], N3 stage (OR 3.05) and/or T4 stage (OR 2.16) have a significantly increased incidence of distant metastasis [40]. Most of these clinicopathological risk factors were based on postoperative histopathological examination and thus were not available for pretreatment decision making. Therefore, most of these risk factors are only useful for deciding on systemic adjuvant treatment and selection for post treatment screening for DM.

For selection of patients for pretreatment screening for DM clinical risk factors are more important. Some identified and validated clinically high risk factors are more than 3 lymph node metastases (cumulative incidence at 5 years 63%), bilateral lymph node metastases (59%), lymph node metastases of 6 cm or larger (51%), low jugular lymph node metastases (61%), regional recurrence (50%) and second primary tumours (39%) [8]. Other reported factors with increased risk for the development of DM are T4 and/or N2 or N3 oropharyngeal, hypopharyngeal and supraglottic squamous cell carcinoma, lymph node involvement of level IV/sublevel VB and MRI-positive nodes with signs of extranodal spread [41-43].

Molecular and radiological characterization techniques

Risk Factors at Initial Diagnosis

Risk of development of DM may also be assessed by molecular characterization of the primary tumour using genomic and proteomic technologies and radiomics. Depending on

the risk of DM it may be justified to screen for DM during follow-up. Several studies have investigated the ability of various molecular markers present in primary tumours to predict the risk of developing distant metastasis. Numerous cellular processes must be co-opted by metastatic tumour cells in order to successfully establish metastatic disease. Theoretically, biomarkers reflecting molecular alterations of these processes at the primary tumour could yield valuable information about its metastatic potential and be informative in estimating individually the chance of distant metastasis in individual patients. Some reports have described biomarkers useful for predicting the metastatic potential of HNSCC. Thus, high E6 gene expression level identifies HPV-positive oropharyngeal SCC patients with fivefold greater risk of distant disease recurrence [44]. Nuclear myoferlin expression is also directly associated with distant metastasis [45]. A meta-analysis of studies using immunohistochemistry for TWIST detection has shown that TWIST expression might have a correlation with clinical features such as low differentiation, advanced clinical stage, presence of lymph node metastasis, distant metastasis and local recurrence [46]. On the other hand, it has been observed that patients with distant metastasis also had high PD-L1 expression [47]. The study of expression patterns of different cell cycle regulatory proteins and members of the EGFR signaling pathway in SCC of the head and neck showed that only pAkt and survivin had a positive correlation with DM [48]. Rodrigo et al. [49] performed an immunohistochemical analysis for a panel of proteins known to participate in cellular processes relevant to metastatic dissemination (E-cadherin, annexin A2, cortactin, FAK, EGFR, p53, and pAkt). Results showed that the loss of E-cadherin expression was significantly correlated with the risk of distant metastasis. Furthermore, Nijkamp et al. [50] also reported that loss of E-cadherin and gain of vimentin may be associated with enhanced migration of tumour cells, leading to higher metastatic risk of HNSCC patients. Rasmussen et al. [51] used a panel of biomarkers with immunohistochemistry to assess the risk of HNSCC patients developing DM and found that a higher expression of p53 was associated with a decreased risk of metastatic failure.

Nevertheless, further studies will be needed to identify and validate in large patient cohorts specific biomarkers useful for the prediction of distant metastatic risk. To date, there are no data mature enough to introduce immunohistochemical expression analysis of proteins in current clinical management. The exploitation of data from the cancer genome consortia will possibly allow us to know the complex interrelationships that govern the development of distant metastasis and to validate a molecular print for clinical application.

Human cancers exhibit strong phenotypic differences that can be visualized noninvasively by medical imaging. Radiomics refers to the comprehensive quantification of tumour phenotypes by applying a large number of quantitative image features, e.g. sphericity shape and gray level nonuniformity on CT. Radiomics converts imaging data into a high dimensional mineable feature space using a large number of automatically extracted data-characterization algorithms [52]. Recently Vallières et al [53] reported on the risk assessment of distant metastasis using radiomics in head and neck cancer patients. By

combining clinical variables with 1615 radiomic features (quantifying tumor image intensity, shape and texture) extracted from pretreatment ^{18}F FDG-PET and CT images from 300 head and neck cancer patients, a predictive model was developed which significantly separates patients into three DM risk groups [53]

Liquid biopsy (material extracted from blood or other fluid) is a minimally invasive method for detecting and monitoring diseases. Among a variety of applications it can be used for early detection during initial diagnostic work-up and, particularly, in follow-up as screening for DM. Blood-based biopsy measurements include circulating tumour cells (CTCs), circulating tumour DNA (ctDNA) and tumour-educated platelets (TEPs)[54].

The detection of tumour cells in blood (CTC) and in bone marrow [disseminated tumour cells (DTC)] provides a promising diagnostic tool especially for those patients at high risk for distant failure. The presence of CTC has been identified as a prognostic factor in different solid tumours. The quantification of CTC and DTC may be used to determine the risk for the development of distant metastatic disease and the associated prognosis [55]. Colnot et al [56] found that in HNSCC patients with 2 or more lymph node metastases the detection of micrometastatic cells by E48 transcripts in bone marrow by reverse transcription-polymerase chain reaction (RT-PCR) was able to identify patients who are at increased risk for the development of DM.

Risk Factors During Follow-up

Free ctDNA may serve as a biomarker for monitoring tumor burden during post-treatment surveillance [57]. Van Ginkel et al [58] showed that detection of tumour specific TP53 mutations in low level Droplet Digital PCR (ddPCR) from HNSCC patients is technically feasible and provides ground for future research on ctDNA quantification for the use of diagnostic biomarkers in the post-treatment surveillance of HNSCC patients [58].

Platelets can also be used as a potential diagnostic tool. External stimuli induce specific splicing of pre-messenger RNAs (mRNAs) in circulating TEPs. Blood platelets contain tumour-derived RNA biomarkers. Using the different platelet mRNA profiles of cancer patients and healthy donors, it is possible to develop a predictive algorithm with high accuracy in separating healthy individuals from cancer patients and identifying (molecular mutational) tumour type [54]. It can be anticipated that in the near future liquid biopsies can be used to detect recurrent disease and select HNSCC patients for screening for distant metastasis during follow-up.

Questions to be answered

Before treatment of oligometastases (metastatectomy or SBRT) and post treatment screening for DM will be implemented in guidelines and routine clinical management of HNSCC patients, many questions still have to be answered. Among these questions, besides diagnostic modality and recognized risk factors, are the following:

Which patients should be selected for these treatments? Factors that may affect this selection include interval between locoregional treatment and diagnosis of distant metastases, and HPV status of the primary tumor.

What should be the frequency of screening during follow-up? At this moment there are no data in favor of any particular post-therapeutic surveillance strategy [59]. Post treatment screening for DM could probably be limited to the first 2 years because in this period most DM are detected [38,42,60].

More research is needed to develop a new protocol for screening for DM after introduction of the concept of treating oligometastases in HNSCC.

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Summary

Head and neck squamous cell carcinoma (HNSCC) accounts for approximately 5% of all malignant tumors worldwide. Two thirds of the patients with HNSCC present with advanced disease. HNSCC's metastasize to regional lymph nodes rather than spread hematogenously. Distant metastases usually occur late in the course of the disease. As locoregional treatment has improved significantly over these last few decades more patients are at risk to develop distant metastases and second primary tumours.

The presence of distant metastases at initial evaluation influences the prognosis and thus treatment selection: since no effective systemic treatment for disseminated HNSCC is currently available, patients with distant metastases are until recently generally not considered curable and often receive only palliative treatment. Overall survival for patients with distant metastases detected at initial screening is significantly poorer compared to patients with distant metastases missed during initial screening and detected during follow-up. Therefore, screening for distant metastases is important to avoid futile extensive treatments.

The aims of this thesis were to evaluate screening for distant metastases in head and neck cancer patients using ^{18}F FDG-PET, chest CT and integrated ^{18}F FDG-PET-CT (**Chapters 2-7**) and to evaluate the clinical practice of this screening in the Netherlands (**Chapter 8**).

In **Chapter 2** a multicenter study is described in which screening for distant metastases in HNSCC patients with high risk factors was performed using ^{18}F FDG-PET and chest CT. The previously identified high risk factors were: three or more lymph node metastases, bilateral lymph node metastases, lymph node metastases ≥ 6 cm, low jugular lymph node metastases, locoregional tumour recurrence and second primary tumours. A total number of 92 patients were included. ^{18}F FDG-PET showed a higher sensitivity to detect distant metastases (53% vs. 37%) and positive predictive value (80% vs. 75%) than chest CT. The combination of ^{18}F FDG-PET and chest CT had the highest sensitivity (63%). ROC analyses revealed that the area under the curve of ^{18}F FDG-PET was significantly higher as compared to chest CT. The addition of ^{18}F FDG-PET to chest CT showed a significant decrease in over-treatment, thus resulting in a decrease of futile mostly extensive treatments in these patients. Therefore, it was concluded that in HNSCC patients with high risk factors, pretreatment screening for distant metastases by chest CT was improved by whole-body ^{18}F FDG-PET.

Cost-effectiveness analyses of the different diagnostic strategies of chapter 2 are described in **Chapter 3**. The costs of the addition of ^{18}F FDG-PET as screening modality were calculated; if distant metastases were found with ^{18}F FDG-PET and missed using chest CT the total costs for curative treatment were deducted. All costs were calculated with the use of clinical scenario analysis. It was concluded that the addition of ^{18}F FDG-PET did not lead to additional costs due to its higher sensitivity in screening for distant metastases which results in a decrease of more expensive futile treatments.

In **Chapter 4** interobserver variability in screening for distant metastases in head and neck cancer patients using ^{18}F FDG-PET and chest CT is investigated. Chest CT and ^{18}F FDG-PET scans of 69 HNSCC patients with high-risk factors who underwent screening for distant metastases were analyzed. All scans were independently read by two experienced radiologists or nuclear physicians who were blinded to the other examinations and follow-up results. The interobserver agreement was determined and expressed in a weighted or unweighted kappa which corrects for agreement by chance. In case of disagreement between the two observers of each modality a final consensus reading was performed. A kappa of 0.516 was found for assessment of size on chest CT. Kappa values for origin (distant metastases or second primary tumour) and susceptibility of 0.406 and 0.512 for chest CT and 0.834 and 0.939 for ^{18}F FDG-PET were found, respectively. Overall, chest CT readings had a reasonable to substantial agreement, while ^{18}F FDG-PET readings showed an almost perfect agreement. These findings suggest that for optimal clinical assessment ^{18}F FDG-PET can be scored by one observer but chest CT should probably more often be scored by two observers in consensus or combined with ^{18}F FDG-PET.

A validation study is described in **Chapter 5**. A test cohort of 47 consecutive HNSCC patients with high risk factors for the development of distant metastases, who had previously undergone ^{18}F FDG-PET and chest CT with a minimum of 12 months follow-up, were retrospectively analyzed. In patients with locoregional control during follow-up the sensitivity and specificity were 55% (95% CI: 23-83%) and 97% (95% CI:82-99%) respectively for chest CT, 55% (95% CI:23-83%) and 100% (95%CI:88-100%) respectively for ^{18}F FDG-PET and 73% (95%CI:39-94%) and 100% (95%CI:88-100%) respectively for the combination of ^{18}F FDG-PET and CT. The in chapter 2 proposed algorithm was considered to have been validated. In this algorithm all ^{18}F FDG-PET positive scans for distant metastases (regardless of interpretation of a solid lung lesion on CT) and CT scans with suspicious pulmonary lesions of less than 5 mm diameter (regardless of ^{18}F FDG-PET findings) are considered positive for distant metastases.

In **Chapter 6** a retrospective study is described in which previously identified high risk factors for development of distant metastases were validated and the impact of time of detection of distant metastases on survival was evaluated. From a total of 301 HNSCC patients with high risk factors (three or more lymph node metastases, bilateral lymph node metastases, lymph node metastases ≥ 6 cm, low jugular lymph node metastases, locoregional tumour recurrence and second primary tumours) who were scheduled for extensive treatment and underwent pretreatment screening on distant metastases using chest CT and/or whole body ^{18}F FDG-PET(-CT), the high risk factors, the development and time point of distant metastases and survival were analyzed. Multivariate analysis revealed that bilateral lymph node metastasis was the strongest predictive factor. Locoregional recurrence and second primary tumours were the risk factors associated with the lowest cumulative incidence. If the risk factor locoregional recurrence was split into local en regional recur-

rences, regional recurrence was associated with a substantially higher risk than local recurrence. The validity of three or more lymph node metastases, bilateral lymph node metastases, low jugular lymph node metastases and regional recurrence as high risk factors for the development of distant metastases was confirmed. The more high risk factors a patient had the lower the 5-year distant metastases free survival was. The detection of distant metastases by pretreatment screening worsens the overall survival as compared to distant metastases detected during follow-up.

A retrospective cohort study is described in **Chapter 7**. In literature different intervals in follow-up term are used as reference standard to calculate sensitivity of screening modalities when screening for distant metastases in HNSCC patients. Longer follow-up intervals result in a significant decrease of reported sensitivities. In this study 46 HNSCC patients with high risk factors to develop distant metastases who underwent pretreatment screening with ^{18}F FDG-PET/CT were retrospectively analyzed using different reference standards. In 16 patients (35%) distant metastases were detected during screening (6 patients) or during a mean follow-up of 39.4 months (10 patients). The sensitivity and negative predictive value were 83.3 and 97.2% when 6 months, 60.0 and 89.9% when 12 months and 37.5 and 72.2% when 30 months follow-up were used as reference standard, respectively. The outcome was comparable with reported studies with similar reference standards. This critical appraisal on the reference standards used in our and reported studies shows room for improvement for the detection of distant metastases to refrain more patients from unnecessary extensive locoregional treatment for occult metastatic HNSCC.

Chapter 8 describes a survey which was performed among the eight centers of the Dutch Head and Neck Society treating head and neck cancer in the Netherlands. The survey was performed with the same questionnaire which was used 10 years ago. The response rate was 100%. ^{18}F FDG-PET-CT and contrast-enhanced chest CT as screening modalities for the detection of distant metastases were routinely used. Compared to the prior survey a reduction of variation in indications and diagnostic techniques used for screening for distant metastases was observed during the last 10 years. Notably all but one center reported they would refrain from extensive treatment if a HNSCC patient would develop clinically manifest distant metastases within 6 months. Although the sensitivity of the diagnostic pathway needs to be improved, most centers were satisfied with the current diagnostic pathway.

In this thesis screening for distant metastases in HNSCC patients is investigated. To avoid futile extensive treatments in patients with high risk factors for the development of distant metastases screening should preferably be performed using a diagnostic tool with the highest sensitivity and accuracy. The combination of chest-CT and whole-body ^{18}F FDG-PET-CT is currently the best available method for screening for distant metastases in HNSCC patients. However, there still is room for improvement.

Samenvatting

Plaveiselcelcarcinomen van het hoofd-halsgebied (HHPCC) nemen ongeveer 5% van alle maligne tumoren wereldwijd voor hun rekening. Twee derde van de patiënten met HHPCC presenteren zich in een vergevorderd ziektestadium. HHPCC's metastaseren met voorkeur naar regionale lymfklieren in plaats van hematogeen.

Afstandsmetastasen presenteren zich meestal laat in het ziekteproces. Gezien de significante vooruitgang van locoregionale behandelingen in de afgelopen decaden hebben patiënten een hoger risico om afstandsmetastasen en tweede primaire tumoren te ontwikkelen.

De aanwezigheid van afstandsmetastasen bij initiële evaluatie beïnvloedt de prognose en dus de keuze van de behandeling; omdat er geen effectieve systemische behandeling is voor uitgezaaide HHPCC's, worden patiënten met afstandsmetastasen tot op heden in het algemeen als incurabel beschouwd en ondergaan slechts een palliatieve behandeling. De algehele ('overall') overleving voor patiënten met afstandsmetastasen gedetecteerd tijdens initiële screening is significant slechter vergeleken met patiënten met afstandsmetastasen die gemist zijn bij initiële screening en gedetecteerd zijn tijdens de follow-up. Om deze reden is het belangrijk om te screenen op afstandsmetastasen bij eerste presentatie en zodoende overbodige uitgebreide behandelingen te voorkomen.

De doelen van dit proefschrift waren het evalueren van de screening op afstandsmetastasen bij hoofd-halskankerpatiënten met ^{18}F FDG-PET van het gehele lichaam, CT-scan van de thorax en geïntegreerde ^{18}F FDG-PET-CT (**Hoofdstukken 2-7**) en het evalueren van de klinische toepassing van deze screening in Nederland (**Hoofdstuk 8**).

In **Hoofdstuk 2** wordt een prospectieve multicenter studie beschreven waarin de screening op afstandsmetastasen in HHPCC-patiënten met hoog-risicofactoren is verricht middels ^{18}F FDG-PET en CT-thorax. Deze eerder gevonden hoog-risicofactoren waren: 3 of meer lymfkliermetastasen, bilaterale lymfkliermetastasen, lymfklier-metastasen ≥ 6 cm, laag jugulaire lymfkliermetastasen, locoregionaal tumorrecidief en tweede primaire tumoren. Een totaal aantal van 92 patiënten werd geïnccludeerd. ^{18}F FDG-PET had een hogere sensitiviteit om afstandsmetastasen te detecteren (53% vs. 37%) en hogere positief voorspellende waarde (80% vs. 75%) dan CT-thorax. De combinatie van ^{18}F FDG-PET en CT-thorax had de hoogste sensitiviteit. ROC analyses toonden dat de oppervlakte onder de curve van ^{18}F FDG-PET significant hoger was in vergelijking met CT-thorax. De toevoeging van ^{18}F FDG-PET aan CT-thorax toonde een significante afname in overbehandeling, resulterend in een afname van overbodige en voornamelijk uitgebreide behandelingen in deze patiënten. Hieruit werd geconcludeerd dat in HHPCC patiënten met hoog-risicofactoren voor de locoregionale behandeling screening op afstandsmetastasen middels CT-thorax verbeterd werd door de toevoeging van ^{18}F FDG-PET.

Kosteneffectiviteit analyses van de verschillende diagnostische strategieën van hoofdstuk 2 worden beschreven in **Hoofdstuk 3**. De kosten van de toevoeging van ^{18}F FDG-PET als screeningsmodaliteit werden berekend; indien afstandsmetastasen werden gevonden

met ^{18}F FDG-PET en deze waren gemist met CT-thorax dan werden de totale kosten van de curatieve behandeling in mindering gebracht. Alle kosten werden berekend met gebruik van een klinische scenario analyse. Er werd geconcludeerd dat de toevoeging van ^{18}F FDG-PET niet leidde tot additionele kosten door de hogere sensitiviteit bij het screenen op afstandsmetastasen resulterend in een afname van (vaak dure) overbodige behandelingen.

In **Hoofdstuk 4** is de interobserver-variatie bij het screenen op afstandsmetastasen bij hoofd-halskankerpatiënten met gebruik van ^{18}F FDG-PET en CT-thorax onderzocht. CT-thorax en ^{18}F FDG-PET scans van 69 HHPCC-patiënten met hoog-risicofactoren die screening op afstandsmetastasen ondergingen werden geanalyseerd. Alle scans werden onafhankelijk beoordeeld door twee ervaren radiologen of nucleair geneeskundigen met blinding voor de resultaten van andere onderzoeken en follow-up. De interobserver-overeenstemming werd bepaald en uitgedrukt in een gewogen en ongewogen kappa welke corrigeert voor overeenstemming op basis van toeval. In het geval er geen overeenstemming kon worden bereikt tussen de twee beoordelaars van elke onderzoek modaliteit werd een definitieve consensusbeoordeling verricht. Een kappa van 0.516 werd gevonden voor de bepaling van grootte van de afwijking op CT-thorax. Kappa-waarden voor aard (afstandsmetastasen of 2^e primaire tumor) en verdenking maligne aspect van 0.406 en 0.512 voor CT-thorax en 0.834 en 0.939 voor ^{18}F FDG-PET, respectievelijk, werden gevonden. Hieruit blijkt dat in het algemeen de beoordelingen van CT-thorax een redelijke tot substantiële mate van overeenstemming hadden, terwijl ^{18}F FDG-PET beoordelingen een bijna perfecte overeenstemming toonden. Deze bevindingen suggereren dat voor een optimale klinische beoordeling ^{18}F FDG-PET gescoord kan worden door een beoordelaar, maar CT-thorax mogelijk door 2 beoordelaars gescoord zou moeten worden in consensus of gecombineerd met ^{18}F FDG-PET.

Een validatie studie is beschreven in **Hoofdstuk 5**. Een cohort van 47 opeenvolgende HHPCC patiënten met hoog-risicofactoren voor de ontwikkeling van afstandsmetastasen, welke eerder screening ondergingen middels ^{18}F FDG-PET en CT-thorax met een minimum follow-up van 12 maanden, werden retrospectief geanalyseerd. Bij patiënten met loco-regionale controle gedurende de follow-up werden respectievelijk een sensitiviteit en specificiteit van 55% (95% CI: 23-83%) en 97% (95% CI:82-99%) voor CT-thorax, 55% (95% CI:23-83%) en 100% (95% CI: 88-100%) voor ^{18}F FDG-PET, en 73% (95% CI:39-94%) en 100% (95% CI:88-100%) voor de combinatie van ^{18}F FDG-PET en CT-thorax. Het in hoofdstuk 2 voorgestelde algoritme werd derhalve als gevalideerd beschouwd. In dit algoritme worden alle ^{18}F FDG-PET positieve scans op afstandsmetastasen (ongeacht de interpretatie van een solide long laesie op CT) en CT scans met verdachte pulmonaire laesies van minder dan 5 mm doorsnede (ongeacht de bevindingen op ^{18}F FDG-PET) beschouwd als positief op de aanwezigheid van afstandsmetastasen.

In **Hoofdstuk 6** is een retrospectieve studie beschreven waarin de eerder geïdentificeerde hoog-risicofactoren voor het ontwikkelen van afstandsmetastasen werden gevalideerd en de impact van tijd bij het detecteren van afstandsmetastasen op de overleving werd geëvalueerd. Bij een totaal van 301 HHPCC-patiënten met hoog-risicofactoren (drie of meer lymfklieren, bilaterale lymfklieren, lymfklieren ≥ 6 cm, laag jugulaire lymfklieren, locoregionaal tumor recidief en 2^e primaire tumoren) welke gepland waren voor extensieve behandeling en voor behandeling screening op afstandsmetastasen ondergingen middels CT-thorax en/ of 'whole body' ¹⁸FDG-PET(-CT) werden de hoog risicofactoren, de ontwikkeling van en tijdstip van detectie van afstandsmetastasen en de survival geanalyseerd. Multivariaat analyse toonde dat bilaterale lymfkliermetastasen de sterkst voorspellende factor was. Locoregionaal recidief en tweede primaire tumoren waren de risicofactoren geassocieerd met de laagste cumulatieve incidentie. Wanneer locoregionaal recidief werd opgesplitst in lokaal en regionaal recidief, bleek het regionaal recidief geassocieerd te zijn met een substantieel hoger risico dan lokaal recidief. De hoog-risicofactoren op het ontwikkelen van afstandsmetastasen drie of meer lymfkliermetastasen, bilaterale lymfklier-metastasen, laag jugulaire lymfkliermetastasen en regionaal recidief werden hiermee bevestigd. Hoe meer hoog risicofactoren een patiënt had des te lager de 5-jaar afstandsmetastase-vrije overleving was. De detectie van afstandsmetastasen tijdens screening voor de behandeling was geassocieerd met een slechtere overall overleving in vergelijking met wanneer de afstandsmetastasen gedurende de follow-up werden gedetecteerd.

Een retrospectieve cohort studie is beschreven in **Hoofdstuk 7**. In de literatuur worden verschillende intervallen van follow-up gebruikt als gouden standaard om de sensitiviteit te berekenen van screeningsmodaliteiten bij het screenen op afstandsmetastasen bij HHPCC-patiënten. Langere follow-up intervallen resulteren in een significante afname van gerapporteerde sensitiviteit. In deze studie werden 47 HHPCC-patiënten met hoog-risicofactoren voor het ontwikkelen van afstandsmetastasen die voor de behandeling screening ondergingen middels ¹⁸FDG-PET/CT retrospectief geanalyseerd met gebruik van verschillende gouden standaarden. Bij 16 patiënten (35%) werden afstandsmetastasen gedetecteerd tijdens screening (6 patiënten) of gedurende een gemiddelde follow-up van 39.4 maanden (10 patiënten). De sensitiviteit en negatief voorspellende waarde waren respectievelijk 83.3 en 97.2% bij 6 maanden, 60.0 en 89.9% bij 12 maanden en 37.5 en 72.2% bij 30 maanden follow-up als gouden standaard. De uitkomst was vergelijkbaar met beschreven studies met soortgelijke gouden standaarden. Deze kritische evaluatie toont ruimte voor verbetering van de detectie van afstandsmetastasen om meer patiënten overbodige uitgebreide locoregionale behandelingen te onthouden.

Hoofdstuk 8 beschrijft een enquête welke gehouden is bij de acht centra van de Nederlandse Werkgroep Hoofd-Hals Tumoren (NWHHT) die HHPCC behandelen in Nederland. De enquête is verricht met dezelfde vragenlijst die 10 jaar geleden reeds gebruikt is. Het

responspercentage was 100%. ¹⁸FDG-PET-CT en CT-thorax met contrast als screeningsmodaliteit voor de detectie van afstandsmetastasen werden routinematig verricht. Vergelijken met de eerdere enquête is er een reductie waargenomen in de variatie van indicaties en diagnostische technieken welke gebruikt werden om te screenen op afstandsmetastasen de afgelopen 10 jaar. Opgemerkt dient te worden dat op één centrum na alle centra aangaven zich te onthouden van extensieve behandeling in een HHPCC-patiënt indien klinisch manifeste afstandsmetastasen zouden ontwikkelen binnen 6 maanden. Ondanks dat de sensitiviteit van het diagnostische traject nog verbeterd dient te worden, gaven de meeste centra aan tevreden te zijn met het huidige diagnostische traject.

In dit proefschrift is de screening op afstandsmetastasen onderzocht. Om onnodige uitgebreide locoregionale behandelingen te voorkomen bij patiënten met hoog-risicofactoren voor het ontwikkelen van afstandsmetastasen zou het screenen bij voorkeur verricht dienen te worden met gebruik van een diagnostische test met de hoogste sensitiviteit en accuraatheid. De combinatie van CT-thorax en 'whole body'¹⁸FDG-PET is tegenwoordig de beste methode voor het screenen op afstands-metastasen bij HHPCC-patiënten. Desondanks is er nog altijd ruimte voor verbetering.